

Summary of Research Activities by Disease Category

Life Stages, Human Development, and Rehabilitation

The development of a vaccine for Haemophilus influenza type b (Hib) is one of NIH's important contributions to public health. Work on this vaccine began several decades ago when NIH intramural researchers Drs. John B. Robbins and Rachel Schneerson were investigating ways to protect infants and young children from Hib. At the time, this often-fatal bacterial infection was the leading cause of meningitis (inflammation of the brain) among children under the age of 5 in the United States. Even with effective antibiotic treatment, 5 percent of the 20,000 children who contracted Hib each year died; about 30 percent were left with intellectual and developmental disability (IDD), deafness, or seizures. Hib meningitis was the leading cause of acquired IDD in the Nation at that time. With the help of research colleagues Drs. David Hamilton Smith and Porter Warren Anderson, Robbins and Schneerson developed a vaccine that proved effective in combating Hib. And, unlike previous attempts at a Hib vaccine, the Robbins-Schneerson version was effective in infants, the population that needed the most protection. Since the vaccine was licensed in 1987, Hib cases have been disappearing rapidly. Today, fewer than 100 cases of invasive Hib infection, almost none with meningitis, occur in the United States each year. This research has virtually eliminated the leading cause of acquired IDD in the United States. With widespread use of the vaccine, it may be possible to end this disease throughout the world.

Introduction

Interactions among biological processes and physical and psychosocial factors in the environment shape an individual's health and functional capacities from the earliest formation of cells, tissues, organs, and organ systems through childhood, adulthood, and old age. NIH research focuses on healthy developmental processes and the ways in which these processes go off track, causing or contributing to much of the Nation's heavy burden of disease and disability. Some disorders of altered developmental processes, such as neural tube defects, are apparent at birth. Others, including intellectual and developmental disabilities, obesity, cardiovascular and metabolic diseases, cancers, mental illnesses, and dementias, may not emerge until months, years, or decades later.

Human development progresses most rapidly during gestation and early childhood but continues throughout the course of life. Each developmental stage lays the foundation for health or illness in subsequent stages. This means that the developmental aspects of NIH research have critical implications for public health. Understanding precisely what happens during developmental "windows" of heightened sensitivity to infections, toxic exposures, personal behaviors, and a host of other environmental factors is essential to learning how and when to intervene most effectively to prevent or lessen chronic and disabling conditions. For example, NIH-supported researchers recently showed that early intervention for 2-year-olds with speech delay can help most of them catch up with their more talkative peers by age 7.^{[131](#)} In another example, NIH-supported research indicates that older people can delay some losses of function associated with the normal aging process with moderate exercise, satisfactory nutrition, and certain other personal behaviors.^{[132](#)}

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This area of NIH research also encompasses medical rehabilitation, including tissue regeneration, to optimize the functioning of individuals with disabling conditions. Medical rehabilitation research is the study of physiologic mechanisms, methods of treatment, and devices that serve to improve, restore, or replace underdeveloped, lost, damaged, or deteriorated function. A key aspect of medical rehabilitation research is its focus on the effects of functional problems on the whole person, rather than a single organ system. Thus, it views the individual in the context of a dynamic system of interacting variables, including organic, psychosocial, and environmental factors.

The role of developmental processes in the risks for common and rare disorders and in rehabilitation science means that the scope of NIH research in life stages, human development, and rehabilitation is quite broad. This research area includes basic research on molecular and cellular processes to gain insights into the trajectories of human development and disease and even to harness developmental processes such as cell differentiation for therapeutic and rehabilitative uses. This research area also includes the collection and analysis of data over the lifespan or over a specific period of interest, such as childhood or aging. Such studies can suggest the relative contributions, to health or to specific disorders, of environmental exposures and ongoing developmental and disease processes. Also included are studies of specific disorders with an emphasis on an individual's life stage or developmental status.

As the Institute with statutory responsibility for child health and human development research, NICHD conducts and supports research programs in reproductive health and in the developmental processes that begin before conception and continue through adolescence. As the Institute with statutory responsibility for research on aging, NIA conducts and supports research on both the maintenance and loss of functions during the aging processes, diseases associated with aging, and the problems and needs of older individuals and their caregivers. NINR supports research across all life stages to build the scientific foundation for clinical practice and managing and eliminating symptoms caused by illness, and it also is the designated lead NIH Institute for end-of-life research. NIEHS focuses on the influences of environmental agents on the development and progression of specific diseases.

Numerous other ICs support life stages, human development, and rehabilitation research in cancer, diabetes, musculoskeletal and neurological disorders, and other areas relevant to their missions. ORWH, among its many roles, works across all ICs to develop opportunities for and support research and training opportunities for studying disorders relevant to women's health across the lifespan and sex and gender differences in disease. Mission-specific rehabilitation research is supported by multiple Institutes, including NIA, NIBIB, NICHD, NIDCD, NIDCR, and NINDS. A focal point for this research is NICHD's National Center on Medical Rehabilitation Research, which emphasizes the rehabilitation and lifelong care of people with physical disabilities resulting from stroke, injury, and other disorders.

¹³¹ Rice ML, et al. *J Speech Lang Hear Res* 2008;51:394-407. PMID: 18367685.

¹³² For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-09-009.html>.

Burden of Illness and Related Health Statistics

Many sections of this report include data on the burden of illness of specific conditions in which developmental-environmental interactions are or may be implicated. Comprehensive data on the total burden of these conditions do not appear to be available. The magnitude of this burden, however, is

suggested by the complex problem of obesity and its associated conditions, including type 2 diabetes, cardiovascular disease, pregnancy complications, certain cancers, osteoarthritis, liver and gall bladder disease, and depression. The Centers for Disease Control and Prevention estimates the prevalence of obesity among individuals ages 20 years and older in the United States as 31.4 percent and the prevalence of obesity plus overweight as 66 percent. Overweight and obesity also exert a substantial economic toll on the United States, with the combination of direct health care costs plus indirect costs, such as lost wages caused by illness, estimated to be \$117 billion for the year 2002.¹³³

Although the mechanisms are not well understood, the developmental dimensions of obesity are evident in several types of data that implicate, for example, the uterine environment in birth defects and other significant problems. Maternal obesity during pregnancy appears to independently interfere with embryonic development, leading to increased risks of congenital abnormalities, particularly neural tube defects (NTDs). Conventional folic acid supplementation during pregnancies of obese women appears to be ineffective in preventing NTDs.¹³⁴ Children of mothers who were obese during pregnancy are at significantly higher risk of developing the metabolic syndrome, a combination of conditions that include obesity and cardiovascular and metabolic disorders, notably type 2 diabetes, in childhood.¹³⁵ Children of mothers with type 2 diabetes during pregnancy, a condition associated with obesity, are at elevated risk for a range of neurodevelopmental problems that affect childhood motor functioning, attention span, activity level, and learning ability. To some investigators, these symptoms suggest a possible association with later-emerging schizophrenia.¹³⁶

Obesity and its associated medical conditions so compromise quality of life and escalate medical costs that finding effective interventions, especially for early stages of life, is a major health priority. A recent estimate placed the costs of inpatient care alone of children with an obesity diagnosis (primary or secondary) at \$237.6 million in 2005.¹³⁷ At the other end of the age spectrum, approximately 80 percent of individuals in the United States ages 65 years or older have at least 1 chronic condition and 50 percent have at least 2. Almost half of lifetime expenditures, 48.6 percent, are attributed to the 65-and-older population in the United States.¹³⁸

Estimating the burden of functional limitations for which rehabilitation may be indicated is complicated by lack of consensus on the definition of "disability," appropriate survey measures, and other issues. The Institute of Medicine (IOM) defines disability as impairments in body structure or function, limitations on activities such as dressing and other daily personal care, and limitations on participation in such activities as school and work. IOM reported that between 40 million and 50 million individuals, or about 1 in 7 Americans, have some type of disability.¹³⁹

¹³³ For more information, see <http://win.niddk.nih.gov/statistics/index.htm>; National Center for Health Statistics. *Chartbook on Trends in the Health of Americans*. Health, United States, 2006; Hyattsville, MD: Public Health Service; 2006.

¹³⁴ Ramachenderan J, et al. *Aust N Z J Obstet Gynaecol* 2008;48(3):228-35. PMID: 18532950.

¹³⁵ Boney CM, et al. *Pediatrics* 2005;115(3):e290-6. PMID: 15741354.

¹³⁶ Van Lieshout RJ, Lakshmi LP. *J Psychiatry Neurosci* 2008;33(5):395-404. PMID: 18787655; PMCID: PMC2527714.

¹³⁷ Trasande L, et al. *Health Aff* 2009;28(4):w751-60. PMID: 19589800.

¹³⁸ Alemayehu B, Warner KE. *Health Serv Res* 2004;39(3):627-42. PMID: 15149482. PMCID: PMC1361028.

¹³⁹ Institute of Medicine. Field MJ, Jette AM, ed. *The Future of Disability in America*. Washington, DC: National Academies Press; 2007.

Actual NIH funding support levels for rehabilitation research were [\\$403](#) million in FY 2008, and [\\$404](#) million and [\\$75](#) million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Currently, NIH does not collect the trans-NIH funding data necessary to provide an aggregate figure for expenditures on life stages, human development, and rehabilitation. Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in this investment (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

The goal of NIH life stages, human development, and rehabilitation research is to enable individuals to achieve a full lifespan with the best health and function at every life stage. Understanding complex developmental pathways to health or illness throughout the life course is critical to creating new ways to prevent disease and disability before they become symptomatic, or even preempting the disease process before it starts. Basic, clinical, and translational research all rest on the fundamental concept of developmental science, that the formation and function of cells, tissues, organs, organ systems, and the fully formed individual are sensitive to protective or harmful environmental factors, and especially so at specific stages. These factors include physical agents, such as industrial and agricultural chemicals, tobacco and alcohol, microbial infections, nutritional deficits, and even medical treatments such as pharmaceuticals and radiation. Powerful environmental influences also include behaviors of individuals and of the people with whom a person lives or works, and norms and values of households, families, schools, workplaces, and communities. Sex and gender differences affect developmental trajectories and disease risks. All such factors can have immediate, intermediate, and/or long-term effects on human health and function.

Human Development

In studies of the most fundamental molecular and cellular processes, NIH scientists continually expand understanding of how development typically progresses, what goes awry and why, and how health is affected (also see the section on *Molecular Biology and Basic Sciences* in Chapter 3). For example, "epigenetic" influences on the expression of genes may be critical mechanisms for gene/environment interactions that influence health and development. Understanding these subtle interactions is an essential step toward discovering treatments and preventive strategies. Scientists recently investigated a type of epigenetic modification, known as DNA methylation, by exposing pregnant yellow agouti mice to bisphenol A, an organic compound found in plastics and plastic additives whose safety has been questioned. The scientists found that maternal exposure to the compound altered the coat color in the offspring by decreasing the methylation at a critical point. Moreover, they found that they could reduce this effect by simply supplementing maternal diets with either folic acid or an estrogen-like chemical found in plants.^{[140](#)}

NIH has established the [Roadmap Epigenomics Program](#) to stimulate the creation of important new scientific resources for epigenetics researchers and thus speed progress toward applications that affect human health and common, complex human diseases. A major effort in the program is characterizing the epigenome, that is, creating a catalog of stable epigenetic modifications that occur in the genome (all genes encoded in the DNA). Among other things, Roadmap epigenomics resources may become the basis for studies of diabetes, including the effects of the intrauterine environment on later risk of this disorder.

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Basic research in developmental biology also may enable scientists to harness powerful normal processes in the lives of cells for therapeutic purposes. Research on cell senescence, a prominent mechanism of normal aging, one day may yield understanding of cellular mechanisms that act to block the development of cancer as well as specific characteristics of aging. Goals of human embryonic stem cell research include explaining critical events in early human development that could lead to developing customized regenerative medical interventions. Sex and gender differences affect developmental trajectories and disease risks. Basic research is only one essential component of the NIH portfolio of multiple methodological approaches to understanding human development. For example, with NIH support, investigators are assembling a unique database of anatomical neuroimages of children's developing brains over time. This database also will include clinical, behavioral, demographic, and cognitive data on the children, thus enabling scientists to understand the multiple dimensions of normal human brain development. Such understanding is essential to elucidating intellectual and developmental disabilities, pediatric neurological diseases, and many other disorders that emerge in childhood. The multidecade Baltimore Longitudinal Study of Aging (BLSA) has created a wealth of information that has helped scientists—and the public—understand distinctions between physical changes attributable to the aging process and those caused by disease.¹⁴¹ These data have yielded important insights on, among other things, relationships between age-related changes in the arteries and cardiovascular disease and differences between normal declines in cognitive ability related to age and those associated with Alzheimer's disease (AD) and related conditions.

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¹⁴⁰ Dolinoy DC, et al. *Proc Natl Acad Sci U S A* 2007;104(32):13056-61. PMID: 17670942. PMCID: PMC1941790.

¹⁴¹ For more information, see <http://www.grc.nia.nih.gov/branches/blsa/blsa.htm>.

Life Stages

"Life stages" or "life course" research is a concept that informed landmark epidemiological and longitudinal studies. These studies linked risks of major adult-onset disorders, including diabetes, hypertension, stroke, and heart disease, to environmental influences in utero and in early childhood.¹⁴² NIH research examples in this section illustrate how the life-course research model has expanded to include a greater number of developmental stages and a wide array of environmental factors and conditions of interest, with a goal of determining how—and when—to intervene to prevent or treat disease. NIH-supported investigators at Breast Cancer and Environment Research Centers are studying mammary gland development in animals and young girls to determine vulnerability to environmental agents that may explain emergence of breast cancer in adulthood. Among other projects, researchers are following a population of young girls to see how diet affects adipose (body fat) tissue and may alter hormonal control of sexual maturation. Although the data are mixed, there is some evidence of possible associations among childhood overweight and obesity, early onset of puberty and, in girls, later risk of breast cancer.^{143,144}

NIH-supported research on maternal and childhood obesity seeks to understand complex interactions

among genetic, psychological, physiological, familial, community, and other factors in this major public health problem. The goals of such research include understanding rapid, recent increases in rates of obesity and determining how and when to intervene to achieve lasting effect. NIH findings of high rates of overweight and other major risk factors for type 2 diabetes in middle school students are the basis for current trials of school-based diet and exercise interventions. The goal of the interventions is to decrease the children's short- and longer-term risks for obesity and diabetes. An ongoing study of the potential of substantially reducing caloric intake to prolong human life—as has been demonstrated in animals—has enhanced understanding of exercise as an important component to sustain weight loss. The [Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy \(CALERIE\)](#) found that energy metabolism slows in response to caloric restriction, but that this "metabolic adaptation," which may make weight control more difficult, can be forestalled when exercise is added to dietary restriction.

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The tendencies toward risky behaviors attributed to immaturity of the brain in adolescence makes this developmental stage of interest in studies of substance dependency and addiction. In seeking to understand how developmental stage may influence vulnerability to, or protection from drug abuse, scientists are beginning to understand how a range of environmental variables, including quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics, influence brain development and behavior. Researchers also are testing preventive strategies such as physical activity and interactive Web-based technologies to engage young people. The NIH [Underage Drinking Initiative](#) similarly seeks to understand environmental, biobehavioral, and genetic factors that may influence progression in young people to harmful alcohol use, within the context of overall development. (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2.)

Better understanding of relationships between developmental stages and disease processes may be critical to the efficacy of therapeutic interventions. NIH scientists discovered that the retinal cells of children with the rare eye disorder, Leber congenital amaurosis (LCA), remain viable for several years, providing a window of opportunity to intervene. An early clinical trial already has shown that a gene transfer treatment for affected children is safe and improves visual function.¹⁴⁵ In another example, NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain development, but with a significant delay in maturation of the prefrontal cortex between the ages of 5 and 15 years. Scientists now are investigating the effects of treatment on rates of cortical maturation.

Research that led to universal newborn screening for phenylketonuria and for hypothyroidism and immediate initiation of treatment for affected infants to protect their developing brains has virtually eliminated intellectual and developmental disabilities (IDDs) associated with these conditions. NIH now is funding a major initiative to speed the development of highly efficient technology for screening newborns for very large numbers of additional rare genetic conditions and to accelerate the discovery of treatments for such conditions. This initiative also includes support for networked facilities to translate scientific discoveries quickly into clinical practice.

Other NIH investments in understanding and developing interventions for Fragile X and Down syndromes and other IDDs include support for 14 IDD centers. These centers provide core research resources in genetics and proteomics as well as clinical infrastructure for a wide range of studies. Multiple NIH-supported programs focus on autism and autism spectrum disorders (ASDs). For example, American Recovery and Reinvestment Act funding is being used to accelerate research in such areas as immune and central nervous system interactions that may help to explain the

heterogeneity of ASDs. The Early Autism Risk Longitudinal Investigation (EARLI) is following a large cohort of mothers of children diagnosed with autism who are pregnant or planning another pregnancy. Among planned EARLI analyses are determining whether in utero exposure to certain organic pollutants is associated with autism risk.¹⁴⁶ (Also see the sections on *Neuroscience and Disorders of the Nervous System* in Chapter 2 and *Autism Centers of Excellence* in Chapter 4.)

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Included in NIH research on conditions associated with adult life stages are studies to find and test safe and effective interventions for female pelvic floor disorders and for menopausal symptoms, both of which typically emerge in middle age. A comprehensive Longitudinal Mental Health Tracking System, now under construction, will bring together a wealth of epidemiological information that already is being collected. The new system will enable scientists to track the trajectories of mental disorders as well as their prevalence, incidence, severity, and other data over time.

Research on normal maturational processes may lead to new ways to treat or prevent disorders associated with aging. For example, genetics are known to play a role in the age-related hearing loss (presbycusis) that affects most individuals after age 60. A research team studying gene activity in the inner ear of a mouse model of presbycusis has identified multiple genes that are involved in programmed cell death (apoptosis), and determined that the activity of these genes increased as the mice aged and hearing loss progressed. This research raises the possibility that a drug may one day be developed that could stop or delay apoptosis of sound-detecting cells as they age in the human ear.¹⁴⁷

In other research, NIH is supporting a clinical comparison of the safety and efficacy of two drugs for treating advanced age-related macular degeneration, a leading cause of vision loss in older individuals. A recent NIH review and analysis of its research program on geriatric translational neuroscience included a workshop to identify priority questions relating to causes of mental disorders in older individuals. Studies of age-related cognitive decline, distinct from Alzheimer's disease (AD) and other dementias, have yielded a wealth of data on positive effects of cognitive training, physical exercise, social engagement, stress reduction, and other strategies. The potential of this accumulated evidence prompted NIH to partner with foundations in supporting work to translate findings on cognitive aging into developing interventions that can be tested in clinical trials.

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NIH makes major investments in research to understand onset and progress of AD, the most common form of dementia in aging, and to discover how to slow its progress and, ultimately, to prevent it. An innovative public-private partnership, The Alzheimer's Disease Neuroimaging Initiative (ADNI), has stimulated the development of more sensitive tools for tracking the development and progression of mild cognitive impairment and AD. Other ADNI projects include a genome-wide association dataset of study participants and a longitudinal study of cerebrospinal fluid samples collected from study participants.¹⁴⁸ Another major NIH investment in this area is in AD translational research, including drug discovery, preclinical development, and toxicology services for testing promising therapeutic compounds. Much of NIH's clinical AD research is carried out through the Alzheimer's Disease Cooperative Study (ADCS), conducted by a consortium of centers that are testing how to predict AD development in vulnerable individuals and develop ways to block its emergence or lessen its effects.

ADCS projects include multiple trials of agents that may slow cognitive decline associated with AD, delay the emergence of AD-associated agitation and psychosis, and otherwise treat this devastating disorder.¹⁴⁹ (Also see the section on *Neuroscience and Disorders of the Nervous System* in Chapter 2.)

At all stages of life, individuals with chronic or critical illnesses and their families and clinical caretakers need evidence-based guidance and support in managing chronic illness and transitioning to the end of life. End-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on such issues as: alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-, and disease-specific factors that make each person's experience at the end of life unique. NIH end-of-life research applies biological, behavioral, and social science strategies to advance the understanding of the dynamic interactions of these various factors and to develop interventions that optimize patient and caregiver quality of life across care settings and cultural contexts. NIH recently sponsored an initiative to develop and test interventions to enhance end-of-life and palliative care, which providers can implement across multiple settings, illnesses, and cultural contexts. NIH-supported Centers in Self Management or End-of-Life research are important loci for interdisciplinary research in this area.¹⁵⁰

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¹⁴² Barker DJ. *Clin Sci (Lond)* 1998;95(2):115-28. PMID: 9680492.

¹⁴³ Kaplowitz PB. *Pediatrics* 2008; 121 Suppl 3:S208-17. PMID: 18245513.

¹⁴⁴ Golub MS, et al. *Pediatrics* 2008;121 Suppl 3:S218-30. PMID: 18245514.

¹⁴⁵ Cideciyan AV, et al. *Proc Natl Acad Sci U S A* 2008;30105(39):15112-7. PMID: 18809924. PMCID: PMC2567501.

¹⁴⁶ For more information, see <http://earlistudy.org>.

¹⁴⁷ Tadros SF, et al. *Apoptosis* 2008;13(11):1303-21. PMID: 18839313. PMCID: PMC2829878.

¹⁴⁸ For more information, see <http://www.loni.ucla.edu/ADNI>.

¹⁴⁹ For more information, see <http://www.adcs.org/Default.aspx>.

¹⁵⁰ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-004.html> and <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-005.htm>.

Rehabilitation

The goal of rehabilitation science is to enable individuals with functional impairments associated with congenital disorders, chronic diseases, or events such as stroke or traumatic injury to live full and productive lives, as independently as possible. Developmental stages are a central consideration in this research because differences among age groups, including physiology and physical size, psychosocial trajectories, and expected lifespan, must all be taken into account in rehabilitation interventions.

Goals of research on neural prosthetic devices include improving cochlear implants for people with impaired hearing, and even enabling individuals with paralysis to directly control devices with their brains.

An important focus of rehabilitation research is the interface between medicine and engineering. Scientists explore innovative biomedical technologies and test their capacity to resolve stubborn

medical problems and enhance mobility, sensory, and other functions of individuals with disabling conditions. Among current projects are efforts to develop advanced methods to eliminate infection when lower limb prostheses are attached directly to bones. Early findings on movement control are the basis for a new nerve-muscle graft procedure that significantly improves amputee control of a prosthetic device.¹⁵¹ Goals of research on neural prosthetic devices include improving cochlear implants for people with impaired hearing, and even enabling individuals with paralysis to directly control devices with their brains.¹⁵² NIH also supports development of sophisticated sensors for prosthetic devices and virtual reality systems to enhance rehabilitation.

Basic processes of cellular and molecular development and function offer great potential for rehabilitation research and clinical applications. Scientists are seeking to understand both the mechanisms that underlie functional impairments and the therapeutic potential of such basic developmental processes as cell differentiation. For example, collaborating NIH and Walter Reed Army Medical Center researchers discovered that waste tissue removed surgically to promote the healing of orthopedic injuries and traumatized muscle contains large numbers of progenitor cells that can differentiate into bone, fat, and cartilage cells. This discovery indicates that these tissues can be a new source of cells for a variety of regenerative therapies.¹⁵³ In another example, NIH-supported investigators have developed a type of peptide molecule that can “self-assemble” into tiny, highly specialized fibers in experimental animals. The investigators showed that treating the animals with the fibers following experimentally induced spinal cord injury reduced cell death at the injury site and promoted both motor and sensory fiber regrowth.¹⁵⁴ A major collaboration between the NIH intramural program and the Department of Defense on traumatic brain injury (TBI) research is the new Center for Neuroscience and Regenerative Medicine (CNRM). CNRM research programs will focus on the full spectrum of TBI in patients injured in combat and in civilians with TBI. The Center’s mission includes catalyzing advances in treatment, rehabilitation, and long-term recovery for individuals experiencing TBI.¹⁵⁵ A major collaboration between the NIH intramural program and the Department of Defense on TBI research is the new Center for Neuroscience and Regenerative Medicine (CNRM). CNRM research programs will focus on the full spectrum of TBI in patients injured in combat and in civilians with TBI. The center’s mission includes catalyzing advances in treatment, rehabilitation, and long-term recovery for individuals experiencing TBI.

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¹⁵¹ For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-012.html> and <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-003.html>.

¹⁵² For more information, see <http://www.ninds.nih.gov/funding/research/npp/index.htm> and <http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf>.

¹⁵³ For more information, see http://www.niams.nih.gov/News_and_events/Spotlight_on_Research/2009/progenitor_cells.asp.

¹⁵⁴ Tysseling-Mattiace VM, et al. *J Neurosci* 2008;28(14):3814-23. PMID: 18385339. PMCID: PMC2752951.

¹⁵⁵ For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Neurological_Effects_of_Blast_Injury_Workshop.htm.

Notable Examples of NIH Activity

Key

E = Supported through Extramural research

I = Supported through Intramural research

O = Other (e.g., policy, planning, or communication)

COE = Supported via congressionally mandated Center of Excellence program

GPRA Goal = Government Performance and Results Act

ARRA = American Recovery and Reinvestment Act

IC acronyms in **bold** face indicate lead IC(s).

Human Development

Environmental Epigenetics: Key Mechanisms for Environmental Effects on Gene

Function and Disease: Increasing evidence demonstrates that epigenetic mechanisms—cellular regulatory processes that influence the expression of genes without affecting DNA sequence—play important roles in the pathogenesis of disease. Epigenetic regulation of genes is critically important in normal developmental biology and disease development/progression, and epigenetic modifications can be influenced by environmental exposures (this may be an important mechanism for gene/environment interactions). An early NIH grant program called Environmental Influences on Epigenetic Regulation has resulted in some groundbreaking research on understanding these processes and their roles in health and disease. We know that environmental exposures early in development affect the risk of diseases and dysfunctions that occur in adulthood, many years later. Evidence is growing that exposures *in utero* exert their effects through epigenetic modifications such as DNA methylation (a chemical change to DNA that is associated with silencing gene expression). A recent study in yellow agouti mice demonstrated that maternal exposure to bisphenol A shifted the coat color of the offspring by decreasing methylation in a regulatory portion of the DNA sequence upstream of the coat-color gene. Moreover, maternal dietary supplementation with either folic acid or a phytoestrogen (genistein) inhibited the ability of bisphenol A to reduce DNA methylation. These and other results highlight the importance of this growing area of research for our ability to understand developmental pathogenesis and to design effective interventions.

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 Patel MM, Miller RL. *Curr Opin Pediatr* 2009;21(2):235-42. PMID: 19663041. PMCID: PMC2740858.
 Miller RL. *J Clin Invest* 2008;118(10):3265-8. PMID: 18802486. PMCID: PMC2542856.

- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIEHS**)

Discovery of Novel Epigenetic Marks in Mammalian Cells: The NIH Roadmap Epigenomics Program aims to accelerate the promise of epigenetics into applications that affect human health and a wide range of common complex human diseases by fostering the development of novel resources for research in this field. Epigenetics refers to various modifications to DNA, its associated proteins, or overall chromosome structure that influence whether genes are active or silent, independent of the DNA sequence. Research supported by this program will characterize the "epigenome," a catalog of the stable epigenetic modifications or "marks" that occur in the genome (and which may differ in different types of cells) and its impact on health and disease. One component of the program is an initiative to support research to identify novel epigenetic marks in mammalian cells and assess their role in the regulation of gene activity. It is anticipated that the results of these studies will be translated quickly to global epigenome mapping in human cells (conducted by the Epigenomics Roadmap Program's Reference Epigenome Mapping Centers). The eight research grants funded by this component of the program are expected to yield results that could have a significant impact on our understanding of gene regulation in mammals. In the long term, advances in these areas will enhance our ability to investigate, diagnose, and ameliorate human disease with a significant epigenetic component. For instance, NIH plans to build on these studies to examine the role of epigenomics in diabetes complications and to study effects of the intrauterine environment on the development of diabetes. Other research will examine epigenetic markers of beta cell differentiation.

- For more information, see <http://nihroadmap.nih.gov/epigenomics/initiatives.asp>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIDDK**, Common Fund - all ICs participate)

Developmental Genomics: Neural tube defects are a class of birth defects affecting the brain and spinal cord. Taking folic acid during the weeks before and after conception greatly can reduce a woman's chances of having a child with a neural tube defect. Still, researchers have not yet fully defined the complex relationship that exists between folic acid and vitamin B12, which is essential for synthesizing DNA during growth and development. Because Ireland has a particularly high rate of neural tube defects, NIH researchers collaborated with Irish researchers to look more closely at the role of vitamin B12 in the developmental disorder. They found that children born to women who have

low blood levels of vitamin B12 shortly before and after conception have an increased risk of a neural tube defect. In light of their discovery, researchers said it would be wise for all women of childbearing age to consume the recommended amount of vitamin B12 in addition to folic acid. In a study looking at a different type of birth defect, a trans-NIH team found that about 20 percent of the incidence of isolated cleft lip may be due to a very tiny alteration in a gene involved in facial development. Oral-facial clefts are among the most common birth defects in the United States, arising from disruptions in a dynamic but still poorly understood interplay of genes, diet, and environment.

- Molloy AM, et al. *Pediatrics* 2009;123(3):917-23. PMID: 19255021.
- Rahimov F, et al. *Nat Genet* 2008 Nov;40(11):1341-7. PMID: 18836445. PMCID: PMC2691688.
- For more information, see <http://www.genome.gov/27530477>
- For more information, see <http://www.genome.gov/27528380>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Genomics*
- (E, I) (NHGRI, NICHD, NIDCR)

Basic Research on Human Embryonic Stem Cells: Research on human embryonic stem cells (hESC) promises to elucidate critical events in early human development and may revolutionize customized regenerative medicine. Since FY 2007, NIH has funded five Program Projects on the basic biology of hESC and has developed initiatives to support fundamental research on a new kind of stem cell, called induced pluripotent stem cells (iPS). iPS cells are reprogrammed from adult cells to a pluripotent state remarkably like hESC. These reprogrammed cells offer a powerful approach to generating patient specific stem cells that ultimately may be used in the clinic. NIH sponsored the third in a series of workshops on research and future directions in human embryonic stem cell research in September 2009.

- For more information, see <http://www.nigms.nih.gov/Initiatives/StemCells>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIGMS)

Cell Senescence and Aging: Cell senescence is a mechanism prominent in aging processes and widely considered as an anti-cancer preventive or treatment therapy. Studies focus on such topics as senescence induced by the Ras gene and its potential to halt or slow tumor progression, the role of the retinoblastoma protein pRb in cellular senescence and the development of a wide range of cell types and associated tumors, telomere attrition, the role of oxidative stress, epigenetic regulation, and DNA damage and repair. NIA-supported studies on Werner syndrome (a condition characterized by accelerated aging in children) and the role of the WRN protein in telomere metabolism are improving our understanding of basic cellular mechanisms that act to suppress development of specific aging characteristics and cancer.

- This example also appears in Chapter 2: *Cancer* and Chapter 3: *Molecular Biology and Basic Research*
- (E/I) (NIA)

Magnetic Resonance Imaging; Study of Normal Brain Development: Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to intellectual and developmental disabilities, mental illness, drug abuse, and pediatric

neurological diseases. NIH is creating the Nation's first database of MRI measurements and analytical tools, and clinical and behavioral data to understand normal brain development in approximately 500 children from across the Nation. This large-scale longitudinal study uses several state-of-the-art brain-imaging technologies. Anatomical neuroimaging scans; demographic, medical, cognitive, and behavioral data; and magnetic resonance spectroscopy data now are available to the research community via the NIH MRI Study of Normal Brain Development website.

- For more information, see <http://www.bic.mni.mcgill.ca/niHPD/info/index.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E/I) (NICHD, NIDA, NIMH, NINDS) (GPRA)

Life Stages

Baltimore Longitudinal Study of Aging Celebrates 50 Years: In 2008, the world's most comprehensive and longest-running longitudinal examination of human aging celebrated an astonishing 50 years of ground-breaking research that has transformed the field of geriatrics. Since its establishment in 1958, the NIH-supported Baltimore Longitudinal Study of Aging (BLSA) has provided a wealth of information on the physical consequences of aging and has helped distinguish changes due to aging from those due to disease. Over the past 50 years, BLSA scientists have produced a number of notable findings. For example, they found that, contrary to some stereotypes, people don't become progressively cranky, depressed, or withdrawn as they age. In fact, these traits remain relatively stable for adults after age 30. Another significant BLSA finding has been the discovery of the relationship between PSA (prostate-specific antigen) levels and prostate cancer. BLSA scientists also have elucidated the relationship between age-related changes in the arteries and cardiovascular disease and distinguished normal age-related declines in cognitive ability from those associated with Alzheimer's disease and related conditions.

- For more information, see <http://www.grc.nia.nih.gov/branches/blsa/blsa.htm>
- (I) (NIA)

Adolescent Medicine Trials Network for HIV/AIDS (ATN): Although one-third to one-half of new HIV infections occur among adolescents and young adults, researchers know little about how the complex physiological changes associated with adolescence affect the transmission and course of HIV infection. NIH is supporting a national clinical research network to address the unique challenges and clinical management needs of HIV-positive adolescents and those at risk of infection. Researchers in this network are conducting biomedical, behavioral, and community-based studies to ensure that teens can benefit from the most promising preventive and treatment interventions. For example, one recently published study conducted by the ATN documented that HIV-positive adolescents frequently do not follow prescribed treatment regimens, and the study also identified several factors associated with nonadherence to therapy.

- Rudy BJ, et al. *AIDS Patient Care STDS* 2009;(3):185-94. PMID: 19866536.
- For more information, see <http://www.atnonline.org>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (E) (NICHD, NIDA, NIMH)

Pelvic Floor Disorders: Research supported by NIH showed that nearly one-quarter of all U.S. women were afflicted with one or more pelvic floor disorders. These disorders result when the muscles and connective tissue within the pelvic cavity weaken or are injured, leading to dysfunction of one or more pelvic organs. The NIH-supported Pelvic Floor Disorders Network, with seven sites throughout the country, supports research on the prevention and treatment of pelvic floor disorders. A recent study by the network revealed that a special two-step surgical procedure, compared to standard practice, reduced by half the incidence of urinary incontinence in women with pelvic organ prolapse. In addition, NIH plans to enhance collaborative research among basic scientists and clinician researchers in female pelvic floor disorders, to promote research that has the greatest clinical applicability for addressing unknown aspects of physiology and pathophysiology of pelvic function.

- For more information, see <http://www.pfdnetwork.org/>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-008.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NICHD, NIDDK, ORWH)

Cesarean Delivery vs. Vaginal Birth: The rate of cesarean delivery has risen dramatically over the past 2 decades; in fact, cesarean delivery currently ranks as the most commonly performed surgical procedure in the United States. More research is needed to determine how frequently cesarean deliveries are scheduled for women without medical indications for the procedure, and how these "maternal request" deliveries compare with vaginal delivery in terms of child and maternal health outcomes. Currently, NIH is supporting a Cesarean Registry through the Maternal-Fetal Medicine Units Network. Using data from the registry, researchers found that newborns are at greater risk for health complications after an early cesarean section delivery. Infants delivered by a repeat elective cesarean section at or after 37 weeks, and before 39 weeks, are at significantly increased risk of breathing problems, blood infection, low blood sugar, and admission to the neonatal intensive care unit, similar to those of infants born preterm. These findings continue to support recommendations that clinicians advise their patients to schedule an elective delivery no sooner than 39 weeks of pregnancy. A cesarean delivery that is not medically necessary before this time puts the infant at increased risk of respiratory problems and other adverse health outcomes.

- Tita AT, et al. *N Engl J Med* 2009;360:111-20. PMID: 19129525.
- For more information, see <http://www.bsc.gwu.edu/MFMU/index.html>
- (E) (NICHD)

Most, but Not All, Late-talking Toddlers Catch Up: By age 2, children should have a vocabulary of about 50 words and should begin to combine those words in 2- or 3-word sentences. Children with Specific Language Impairment (SLI) are late talkers with normal scores for nonverbal intelligence and no hearing loss. They demonstrate normal motor skills, social-emotional development, and neurological profiles—the only noticeable gap is in language development. NIH-supported scientists studying language emergence have shown that up to 80 percent of children with SLI at age 2 will catch up by age 7. They also noted that boys are three times more likely than girls to be diagnosed with SLI. Yet when the children were 7 years old, no differences were found between girls and boys. The scientists noted that current study methods are unable to predict which children with SLI will fail to "catch up." They now are working to determine how best to identify children with SLI who need intervention and enrichment to successfully close the language delay gap.

- Rice ML, et al. *J Speech Lang Hear Res* 2008;51(2):394-407.
- (E) (NIDCD)

Pregnancy and Perinatology: NIH continues to support a portfolio of research on high-risk pregnancies and poor pregnancy outcomes, including preterm labor and birth, fetal disorders, Sudden Infant Death Syndrome, maternal health, and stillbirth. Much of this research is conducted through centers and networks that bring together researchers from different disciplines and allow them to study larger numbers of patients. NIH also led the Surgeon General's Conference on the Prevention of Preterm Birth. To immediately implement some key conference priorities, NIH launched a program to identify and address the factors contributing to prematurity among women having their first baby. For those infants born with an adverse pregnancy outcome, NIH plans to support research to develop safe and effective instruments and devices for infants in the neonatal intensive care unit to optimize their care and developmental outcomes. In addition, NIH commissioned an Institute of Medicine (IOM) study to review and update the 1990 IOM recommendations for weight gain during pregnancy. IOM's new pregnancy weight gain guidelines are similar to its 1990 guidelines, except there now is an upper limit on how much weight obese women should gain while pregnant, as gaining too much weight can be risky for both mother and infant.

- For more information, see http://www.nichd.nih.gov/news/resources/spotlight/040908_preterm_prevention.cfm
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-029.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-018.html>
- (E) (NICHD, NHLBI, NIDDK, ORWH)

Newborn Screening: Screening and treating newborns for phenylketonuria and hypothyroidism have virtually eliminated these conditions as a cause of intellectual disability in the United States. NIH recently created a newborn screening translational research network to develop novel technologies and clinical therapies that improve early detection and treatment of newborns with heritable genetic disorders and other congenital conditions. Such a network facilitates and speeds the process by which scientific advances can be translated into clinical practice. Complementing the new research network is an initiative to develop new technologies for newborn screening that can be used to screen for a greater number of conditions than can be screened with current technologies. New technologies would benefit newborn screening programs across the country. In addition, NIH is gathering new data on other conditions, such as Severe Combined Immune Deficiency (a rare form of immune deficiency), to enable researchers to develop screening techniques for this heritable condition.

- (E) (NICHD)

Family Satisfaction During Decisions to Withdraw Life Support: Clinicians in the intensive care unit (ICU) often care for patients who are on several life support measures simultaneously. When such a patient is dying and the decision is reached to withdraw life support, these clinicians may make an imperfect compromise in seeking to balance the complex needs of the patient and the patient's family—they may remove the life support measures one at a time over a period of days, rather than withdrawing all at once. This practice, referred to as sequential withdrawal, may be relatively common, and may have a varying impact on the family's satisfaction with ICU care. The research team

examined the life support withdrawal process for 584 patients who died in the ICU or within 24 hours of discharge from the ICU, and surveyed the family members regarding their perceptions of the care provided. When surveyed 1 to 2 months after the death of the patient, family members of patients who had a short ICU stay reported a lower satisfaction with the ICU care if the withdrawal process was extended over more than 1 day. However, for family members of patients who had a long ICU stay (8 days or more), satisfaction with care increased with a more extended duration of the withdrawal. In addition, family satisfaction with care was higher if the patient was off the ventilator at the time of death. Withdrawal of life support is a complex process that depends on patient and family characteristics; however, sequential withdrawal of life support is a frequent phenomenon that sometimes seems to be associated with family satisfaction.

- Gerstel E, et al. *Am J Respir Crit Care Med* 2008;178(8):798-804. PMID: 18703787. PMCID: PMC2566791.
- For more information, see <http://www.nih.gov/news/health/oct2008/ninr-15.htm>
- For more information, see <http://www.ncbi.nlm.nih.gov/pubmed/18703787>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NINR)

Researchers Developing a Noninvasive Ultrasound Technique to Detect Early Signs of Premature Delivery:

Premature delivery is one of the leading causes of infant mortality in the United States, according to CDC. Currently, clinicians only can attempt to delay delivery once the extensive uterine contractions of labor have been initiated in the final stages of the delivery process. However, because the cervix prepares for delivery weeks to months before labor in a process termed "preterm cervical ripening," an NIH-supported scientist, together with a team of electrical and computer engineers, theorized that a noninvasive ultrasound technique might be used to detect this early warning sign well in advance of premature delivery. The research team developed and tested such a technique using computer simulations in rat tissue samples, followed by studies with live rats. The results were promising in that cervical changes clearly were identifiable using this technique in the tissue samples. With further development, this innovative technique could prove powerful in identifying mothers at risk for premature delivery, thereby reducing or preventing the associated morbidity and mortality.

- Bigelow TA, et al. *J Acoust Soc Am* 2008;123(3):1794-800. PMID: 18345867. PMCID: PMC2637349.
- For more information, see <http://www.ncbi.nlm.nih.gov/pubmed/18345867>
- This example also appears in Chapter 3: *Technology Development*
- (E) (NINR)

Addressing the Heterogeneity of Autism Spectrum Disorders: NIH released a series of Funding Opportunity Announcements (FOAs), supported by funds from the American Recovery and Reinvestment Act of 2009, soliciting applications for 2-year research projects to address the heterogeneity of Autism Spectrum Disorders (ASD). This initiative represents the largest NIH funding opportunity for research on ASD to date and will jump-start many of the short-term objectives set forth in the Interagency Autism Coordinating Committee's Strategic Plan for Autism Spectrum Disorder Research. The FOAs target research in areas such as measurement development, biomarkers, immune and central nervous systems interactions, genetics, environmental risk factors, model development, treatment and intervention, and services research.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-170.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-171.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-172.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-173.html>
- For more information, see <http://www.nimh.nih.gov/science-news/2009/rising-to-the-challenge-nih-will-use-60-million-in-recovery-act-funds-to-support-strategic-autism-research.shtml>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (NIMH, NICHD, NIDCD, NIEHS, NINDS) (ARRA)

Developing Interventions to Improve Palliative Care at the End of Life: The life expectancy of the American people has reached a historic high, but along with increased life expectancy comes an increase in the number of people living with, and dying from, chronic debilitating diseases. Prolonged courses of decline at the end of life, palliative treatment options, and life-sustaining technologies have raised many important research questions within the last decade. In addition, the needs of dying children and their families are coming into greater focus, because death in childhood stands out as a particular tragedy and a unique end-of-life experience for all involved. To address these needs, NIH-supported end-of-life science seeks to understand dying with respect to the needs of dying persons and formal and informal caregivers. It includes research on issues such as: alleviation of symptoms, psychological care, near-death preferences, advance directives, and family decision-making. Likewise, end-of-life research addresses the cultural, spiritual, age-specific, and disease-specific factors that make each person's experience at the end of life unique. In FY 2009, NIH announced a funding initiative to develop and test interventions to enhance end-of-life and palliative care that providers can implement across multiple settings, illnesses, and cultural contexts. NIH made the first awards under this solicitation in late FY 2009.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-09-004.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NINR, NCI)

Workshop on Late-Life Mental Disorders: In FY 2009, NIH undertook a review and analysis of its research program on geriatric translational neuroscience to identify strengths and gaps in current science, and to identify promising new research targets and strategies. As part of this process, a workshop was held that brought together basic and clinical researchers with expertise in aging and mental health. Workshop participants focused on identifying key research questions related to discovering the causes of mental disorders in older populations; charting mental illness trajectories across later-life stage, so as to provide a better evidence base on when, where, and how to intervene; and building the field's scientific infrastructure through training.

- For more information, see <http://www.nimh.nih.gov/research-funding/scientific-meetings/2009/new-perspectives-in-the-translational-neuroscience-of-late-life-mental-disorders.shtml>

- (E) (NIMH)

National Database for Autism Research: The National Database for Autism Research (NDAR) is a collaborative biomedical informatics system created by NIH to provide a national resource to support and accelerate research in autism spectrum disorder (ASD). NDAR hosts human genetic, imaging, and phenotypic research data relevant to ASD, making these data available to qualified researchers. NDAR also has the capability to allow investigators to use NDAR for data sharing among select collaborators in ongoing studies. Through its Data Dictionary, NDAR will foster the development of a shared, common understanding of the complex data landscape that characterizes ASD research. Finally, its architecture facilitates linkage of NDAR with other significant data resources, regardless of their location or ownership and in ways that respect the policies and implementations of those other data resources.

- For more information, see <http://ndar.nih.gov/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E/I) (NIMH, CIT, NICHD, NIDCD, NIEHS, NINDS)

Studies of Diabetes in Youth: NIH and CDC support the [SEARCH for Diabetes in Youth](#) study, which is providing key data on childhood diabetes incidence and prevalence. Recent data from SEARCH revealed unexpectedly high rates of diabetes in youth across most ethnic and racial groups in the United States. SEARCH also estimated that 1 of every 523 youths had physician-diagnosed diabetes in 2001. To address the emerging problem of type 2 diabetes in youth, NIH supports the HEALTHY multicenter study to prevent risk factors for type 2 diabetes in middle-school children. A pilot study for HEALTHY found that an alarmingly high 15 percent of students in middle schools enrolling mainly minority youth had 3 major risk factors for type 2 diabetes; about half of the children were overweight. These data suggest that middle schools are appropriate targets for efforts to decrease risk for obesity and diabetes. Thus, NIH launched the HEALTHY study in 2006. Half of the 42 participating middle schools receive the intervention, which includes changes to school food service and physical education classes, behavior change, and communications campaigns. More than 70 percent of the enrolled students are from minority populations. For children who already have been diagnosed with type 2 diabetes, NIH supports the [Treatment Options for Type 2 Diabetes in Youth \(TODAY\)](#) study, which is comparing three different treatment strategies for children with the disease.

- Mayer-Davis EJ, et al. *Diabetes Care* 2009;32 Suppl 2:S99-101. PMID: 19246580. PMCID: PMC2647691.
- For more information, see <http://www.searchfordiabetes.org/>
- For more information, see <http://www.todaystudy.org/index.cgi>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDDK, CDC)

The Sister Study: Environmental Risk Factors for Breast Cancer: The NIH Sister Study prospectively examines environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 sisters of women who have had breast cancer. The frequency of relevant genes and shared risk factors is greater among sisters, increasing the ability of the study to detect risks. Researchers will collect data on potential risk factors and current health status, and will collect and

bank blood, urine, and environmental samples for future use in studies of women who develop breast cancer or other diseases compared with those who do not. Analysis of new cases will assess the separate and combined effects of environmental exposures and genetic variations that affect estrogen metabolism, DNA repair, and response to specific environmental exposures. Future analyses will focus on known and potential risk factors like smoking, occupational exposures, alcohol, diet and obesity, and include analysis of phthalates, phytoestrogens, metals, insulin, growth factors, vitamins and nutrients, and genes in blood and urine. The study also allows investigators to examine a wide range of health outcomes of relevance to women, and to create a framework from which to test new hypotheses as they emerge. In addition to its focus on genetic and environmental causes of breast cancer, the prospective Sister Study tracks changes in health status over time. Among the chronic diseases currently studied are uterine fibroids and endometriosis, rheumatoid arthritis and other autoimmune diseases, thyroid disease, asthma, and cardiovascular diseases. As the cohort ages, the Sister Study will address aging-related health outcomes including osteoporosis, Parkinson's disease, and age-related cognitive decline.

- For more information, see <http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/sister/index.cfm>
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E/I) (NIEHS, NCMHD)

New Interventions for Menopausal Symptoms: Women going through the menopause transition may experience a variety of symptoms, ranging from vasomotor symptoms (hot flashes and night sweats) to sleep disturbance, mood disorders, loss of sexual desire, and vaginal dryness. As many as two-thirds of all women report vasomotor symptoms, and more than 85 percent report at least 1 menopausal symptom. For the 25 percent of symptomatic women who are burdened severely, the resulting discomfort greatly diminishes their quality of life. Until recently, menopausal hormone therapy (MHT) using estrogen has been the therapy of choice for relieving menopausal symptoms. But after 2002 and the release of findings from the Women's Health Initiative and other studies showing that MHT can be associated with an increased risk of serious health problems such as blood clots, stroke, heart disease, breast cancer and cognitive impairment, women and their health practitioners have been in search of alternative strategies to improve menopausal quality of life. NIH has established the Menopausal Symptoms: Finding Lasting Answers for Sweats and Hot Flashes (MS FLASH) initiative to conduct collaborative studies on interventions for menopausal vasomotor symptoms. A variety of interventions currently are under study, including yoga, exercise, paced respiration, and other hormonal and nonhormonal treatments.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-08-004.html>
- (E) (NIA, NCCAM, NICHD, ORWH)

Ginkgo Evaluation of Memory (GEM) Study Shows No Benefit in Preventing Dementia in the Elderly: Dementia is a loss of brain function that causes serious changes in memory, personality, and behavior. Alzheimer's disease, the most common form of dementia in older people, affects as many as 4.5 million Americans. Some people use extracts of leaves from the *Ginkgo biloba* tree in an effort to prevent or treat Alzheimer's and other types of dementia. NIH-supported

researchers tested ginkgo in a large sample of older adults to see whether it could prevent or delay the onset of dementia, particularly Alzheimer's. The study enrolled 3,069 participants ages 75 or older who had normal cognition or mild cognitive impairment. For about 6 years, they took twice-daily doses (120 milligrams) of either ginkgo extract or a placebo. The study found that ginkgo did not lower the overall incidence of dementia or Alzheimer's. Nevertheless, the study demonstrates the feasibility of large dementia prevention trials in older adults, and provides useful information about how to design and conduct such trials. The results of this study confirm the importance of randomized trials in determining therapeutic benefit of new approaches to dementia and Alzheimer's disease. The results also provide a wealth of information that will be valuable in designing future clinical trials. Future analyses of the data will provide additional information on ginkgo's possible effects on cardiovascular disease, cancer, depression, and other age-related conditions. They also may identify subgroups at greater risk for developing dementia.

- Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19017911. PMCID: PMC2823569.
- For more information, see <http://nccam.nih.gov/research/results/gems/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E) (**NCCAM**, NHLBI, NIA, NINDS, ODP/ODS)

Alzheimer's Disease Cooperative Study (ADCS): Much of the AD-related clinical research supported by NIH takes place through the ADCS. The study involves a consortium of centers in the U.S. and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of AD or predict development of the disease in vulnerable people. To date, approximately 4,600 people have participated in the trials. Five new trials are underway through ADCS. These include: (1) a trial to examine whether treatment with DHA, an omega-3 fatty acid, will slow decline in AD; (2) a multicenter trial to evaluate home-based assessment methods for AD prevention research in people age 75 or older; (3) a trial to evaluate the efficacy and safety of 18 months of treatment with the drug PF-04494700 (TTP488), an oral compound formulated to prevent amyloid beta from binding to a specific brain receptor; (4) a trial of valproate, an anticonvulsant drug, to determine its ability to delay the emergence of agitation and psychosis and possibly the clinical progression of AD; and (5) a trial of intravenous immunoglobulin, which contains naturally occurring antibodies against beta-amyloid, to establish its clinical utility for treating AD. This program is a cornerstone of the NIH GPRA goal to: "By 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- For more information, see <http://www.adcs.org/Default.aspx>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIA**) (GPRA)

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial magnetic resonance imaging, positron emission tomography, or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease (AD). ADNI has reached its target enrollment of 800 participants, and supported development of a number of tools and methods now in use in the United States as well as in Japan, the European Union, and Australia. Other expansions include a genome-wide association study of ADNI participants scheduled to provide the most

extensive and robust dataset of its kind in the AD field; a study that allows for longitudinal analysis by the collection of additional cerebrospinal fluid from participants over several years; and a study exploring the use of PET and Pittsburgh Compound B (PIB) as a tool for developing biochemical markers. A recent ADNI study confirmed that certain changes in biomarker levels in cerebrospinal fluid may signal the onset of mild Alzheimer's and established a method and standard of testing for these biomarkers.

- For more information, see <http://www.loni.ucla.edu/ADNI>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (NIA, NIBIB)

Interventions to Remediate Age-Related Cognitive Decline: Age-related cognitive decline distinct from dementia will affect most older individuals to some extent and has a direct impact on their independence and vitality. Cognitive training, physical exercise, enhancement of self-efficacy, social engagement, diet, environmental enrichment, and stress reduction have all been shown to have positive effects on cognition; however, the quality of this evidence varies widely across studies. NIH, in partnership with the McKnight Brain Research Foundation in conjunction with the Foundation for NIH, has initiated a program to convert insights from previous work in cognitive aging into feasible intervention strategies that can be tested in randomized clinical trials. The program's primary goal is to support the initial development and pilot testing of behavioral interventions (individually and in combination) to establish their feasibility, the likely strength of their effects, and immediate and short-term efficacy. These early steps should allow these interventions to move to new clinical trials.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-09-009.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (NIA)

Translational Research on Alzheimer's Disease (AD): To move basic research on AD and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. A number of agents are undergoing testing, including antihypertensives, anti-inflammatory drugs, and novel small molecules. In addition, in recent years, NIH-supported basic research has contributed to industry development of new Alzheimer's disease drugs. This program is a cornerstone of the NIH GPRA goal to "by 2013, identify at least one clinical intervention that will delay the progression, delay the onset, or prevent Alzheimer's disease."

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-048.html>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (NIA) (GPRA)

Genes Change How We Hear as We Grow Older: Scientists know that genetics play some role in presbycusis (age-related hearing loss), which affects most individuals greater than 60 years old. But until recently, they have been unable to pinpoint any human gene that may be responsible for

presbycusis. The search for specific genes involved in presbycusis is complicated because many other factors can contribute to the onset of age-related hearing loss, including sound exposure, medications that can damage hearing, the aging brain, and changes in the sound-detecting cells of the inner ear. A research team of NIH-supported scientists looked at gene activity in the inner ear of a particular strain of mice that serves as a model for presbycusis. The team identified eight genes, all of which were involved in apoptosis (programmed cell death), whose activity increased as mice aged and as hearing loss progressed. Apoptosis is the body's way of getting rid of cells that are damaged or no longer needed. Increased or abnormal apoptosis, however, also is involved in many disease processes. The new research is the first demonstration that increased apoptosis also occurs in the aging inner ear. This research offers a potential new area of discovery as scientists work to prevent and even reverse age-related hearing loss. Presbycusis may be treated one day by a drug that stops or delays the sound-detecting cells in the inner ear from undergoing apoptosis as they age.

- Tadros SF, et al. *Apoptosis* 2008;13(11):1303-21.
- For more information, see <http://www.nidcd.nih.gov/health/hearing/presbycusis.asp>
- (E) (NIDCD, NIA)

Breast Cancer and the Environment Research Centers: Researchers at the Breast Cancer and Environment Research Centers (BCERC) are investigating mammary gland development in animals, as well as in young girls, to determine vulnerability to environmental agents that may influence breast cancer development in adulthood. These efforts hopefully will lead to strategies that better prevent breast cancer. The purpose of the centers' program is to answer questions on how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer. Functioning as a consortium at four grantee institutions, the centers bring together basic scientists, epidemiologists, research translational units, community outreach experts, and community advocates. At one center, a sophisticated genomics and proteomics approach explores the impact of estrogenically active chemicals such as TCDD, bisphenol A, and phthalates, during early, critical periods of development. This is facilitated by advanced informatics at another major research institution. At another center, novel approaches to studying the impact of environmental exposures on interactions between epithelial cells and stromal cells are being studied. Normal and cancer-prone mice are being examined during various stages of development to determine the effects of exposure to multiple stressors as researchers are developing more sensitive screens for carcinogenicity. In concert with these studies, an epidemiological multi-ethnic study is examining and following through puberty a cohort of 7- and 8-year-old girls from the Kaiser Foundation Health Plan. Other researchers are studying a population of white and African American public school students to see how diet affects adipose tissue and alters hormonal control of sexual maturation. Endocrine disruptors, irradiation, and psychosocial elements also will be studied for effects.

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- Kouros-Mehr H, et al. *Curr Opin Cell Biol* 2008;20(2):164-70. PMID: 18358709. PMCID: PMC2397451.
- Ewald AJ, et al. *Dev Cell* 2008;14(4):570-81. PMID: 18410732. PMCID: PMC2773823.
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Egeblad M, et al. *Dis Model Mech* 2008;1(2-3):155-67; discussion 165. PMID: 19048079. PMCID: PMC2562195.

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Teitelbaum SL, et al. *Environ Res* 2008;106(2):257-69. PMID: 17976571.

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Santos SJ, et al. *J Steroid Biochem Mol Biol* 2009;115(3-5):161-72. PMID: 19383543. PMCID: PMC2729057.

Yang C, et al. *Reprod Toxicol* 2009;27(3-4):299-306. PMID: 19013232.

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J Health Psychol 2008;13(8):1180-9. PMID: 18987091.

Atkin CK, et al. *J Health Commun* 2008;13(1):3-19. PMID: 18307133.

Kariagina A, et al. *Crit Rev Eukaryot Gene Expr* 2008;18(1):11-33. PMID: 18197783.

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Biro FM, et al. *J Pediatr Adolesc Gynecol* 2009;22(1):3-6. PMID: 19232295. PMCID: PMC2744147.

- For more information, see <http://www.bcerc.org/>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Epidemiological and Longitudinal Studies*, Chapter 3: *Genomics*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (E) (NIEHS, NCI) (GPRA)

Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy

(CALERIE): A large body of research in animals indicates that substantially reducing caloric intake while maintaining optimal nutrition can significantly lengthen life span. The CALERIE study will help to determine if these effects extend to humans. This long-term study began in January 2007 and is ongoing. Recently, CALERIE researchers used state-of-the-art techniques to measure metabolic changes that occur in response to caloric restriction with or without exercise. They found that energy metabolism slows in response to caloric restriction, but the addition of exercise to a caloric restriction regimen may forestall such a "metabolic adaptation," potentially explaining why a combination of dietary restriction and exercise, as opposed to dietary restriction alone, may be the best intervention to sustain weight loss. Overall, these findings provide important information about the mechanisms of weight loss and indicate that exercise may be an important component of a weight loss regimen.

- For more information, see <http://calerie.dcri.duke.edu>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIA)

A Variety of Approaches Help Children Overcome Auditory Processing and Language Problems:

Almost 7 percent of school-age children have difficulties learning and using language. Childhood language impairments can have lifelong effects on an individual's social life, academic career, and job aspirations. Each year, more than 1 million public school children receive interventions to address their language impairments. One very popular intervention is a commercially available software program called Fast ForWord Language (FFW-L; Scientific Learning Corporation, 1998). NIH-supported scientists conducted a randomized controlled trial of more than 200 children with language

impairments, to assess whether those who used FFW-L had greater improvement in language skills than those who used one of two other methods, plus an active control group. The children in all three intervention groups demonstrated statistically significant improvement in both auditory processing and language skills. Thus, FFW-L did not provide a significant advantage over other types of interventions delivered in a similar intensive manner. Surprisingly, children in the active control group, which received individualized attention, instruction, and computerized testing on academic subjects but did not receive language intervention, also demonstrated significant improvement in auditory processing and language skills. This study demonstrated that all four methods improved the children's auditory processing and language skills. The data suggest that intensive programs focusing individualized attention on children with language impairments can improve language skills and preempt lifelong communication difficulties.

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Gillam RB, et al. *J Speech Lang Hear Res* 2008;51(1):97-119. PMID: 18230858.
PMCID: PMC2361096.
- For more information, see http://www.nidcd.nih.gov/news/releases/08/01_30_08.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NIDCD, NICHD)

Brain Matures a Few Years Late in ADHD: NIH-supported research on brain development in children with attention-deficit/hyperactivity disorder (ADHD) showed a normal pattern of brain development, but with a striking delay in cortical maturation. Between ages 5 and 15, the maturation of the prefrontal cortex was found to be delayed by roughly 3 years in children with ADHD compared to age-matched children without the disorder. Current studies now are exploring the effects of treatment on the rate of cortical maturation.

- Shaw P, et al. *Proc Nat Acad Sci U S A* 2007;104(49):19649-54. PMID: 18024590.
PMCID: PMC2148343.
- For more information, see <http://www.nimh.nih.gov/science-news/2007/brain-matures-a-few-years-late-in-adhd-but-follows-normal-pattern.shtml>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (I) (NIMH)

Centers in Self-Management or End-of-Life Research: Future progress in improving the ability of those with chronic disease at all stages of life to manage their own illness, as well as improving the care of patients at the end of life, will require the development of enhanced research capacity, including more trained investigators and expanded institutional resources. In early 2007, NIH solicited applications for the Centers in Self-Management or End-of-Life Research. These Centers are expected to serve as a nexus for the emergence of self-management and end-of-life research as interdisciplinary sciences. They will train investigators from multiple backgrounds and leverage collaborations to increase the quantity and quality of innovative, interventional research projects. To date, six grants have been awarded from this solicitation. These Centers focus on a variety of topics, such as the self-management of chronic illnesses in Hawaii, biobehavioral research in self-management of cardiopulmonary disease, evidence-based practice in the underserved, and end-of-life transition research.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-004.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-07-005.html>
- (E) (NINR)

Childhood and Maternal Obesity: As the maternal and childhood obesity epidemic widens, researchers are trying to understand the interaction among the many complex biological and behavioral factors that contribute to this rise, identify the long-term impact on mother and child, and develop effective interventions to reverse these trends. NIH obesity research, which includes a range of racial and ethnic groups, is examining such topics as:

- Basic research on the physiology, psychology, and genetics of obesity in children.
 - Developing community-based partnerships to prevent and control childhood obesity.
 - Applying computational and statistical methodologies to design and analyze multilevel studies on childhood obesity. Multilevel studies include those that consider the range of biological, family, community, sociocultural, environmental, policy, and macro-level economic factors that influence diet and physical activity in children.
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-09-140.html>
 - For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-023.html>
 - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*
 - (E/I) (NICHD, NCI, NHLBI, OBSSR)

Comparative Effectiveness of Treatments for Common Childhood Eye

Disorder: Convergence insufficiency (CI) is a relatively common vision problem that develops in childhood in which the eyes do not naturally turn inward when focusing on a close-up visual target. Symptoms include eye strain, blurred vision, headaches, and discomfort. CI can adversely affect reading ability and reading comprehension and can have a serious impact on an individual's performance in school, career, and quality of life. Eye care professionals treat CI with various forms of eye exercises, done at home or in the office of a trained therapist, that require children to sustain focus on nearby objects. The Convergence Insufficiency Treatment Trial (CITT) compared the effectiveness of these therapies. Results indicate that the most popular treatment, known as home-based pencil push-up therapy, was no more effective in improving patient's symptoms than a placebo therapy. However, 73 percent of children assigned to a regimen of intensive, office-based therapy combined with home reinforcement did improve significantly compared to the placebo group. Other commonly prescribed home-based regimens also showed some benefit but were only about half as successful as office-based therapy with home reinforcement. Although home-based treatments for CI are appealing because of their simplicity and low cost, these results indicate that office-based treatment combined with home reinforcement is more effective in helping children to achieve normal vision and reducing symptoms.

- Convergence Insufficiency Treatment Trial Study Group. *Arch Ophthalmol* 2008;126(10):1336-49. PMID: 18852411. PMCID: PMC2779032.
- For more information, see <http://archophth.ama-assn.org/cgi/content/full/126/10/1336>
- This example also appears in Chapter 3: *Clinical and Translational Research*

- (E) (NEI)

Comparative Effectiveness Study of Drugs for Age-Related Macular

Degeneration: Lucentis was approved by FDA in 2006 for treatment of advanced age-related macular degeneration (AMD), a leading cause of vision loss in older Americans. Though the drug is safe and effective, it is expensive—approximately \$2,000 per month—and repeated injections are required. Avastin is a similar pharmaceutical but is far less expensive—approximately \$100 per month—and also has been used extensively in treating patients with AMD. Most retinal specialists think that Avastin is a safe and effective alternative to Lucentis. To resolve this question, NIH is funding the Comparison of AMD Treatments Trial (CATT), a multicenter, randomized, clinical trial to compare the safety and efficacy of Avastin and Lucentis, and to explore less-frequent treatment schedules for both drugs. The first participants were randomized in early 2008. If Avastin proves to be comparable to Lucentis, the cost savings could reach \$2-3 billion per year. Less frequent treatment schedules also would lower costs, reduce treatment risk, and improve patient quality-of-life.

- For more information, see <http://www.nei.nih.gov/news/pressreleases/022208.asp>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NEI)

Demographic and Economic Studies of Aging: NIH supports a number of studies on the demographic and economic changes in our society. The Health and Retirement Study (HRS) is the leading source of combined data on health and financial circumstances of Americans over age 50 and a valuable resource to follow and predict trends and help inform policies for an aging America. Now in its 16th year, the HRS follows more than 20,000 people at 2-year intervals and provides researchers with an invaluable and growing body of multidisciplinary data on the physical and mental health of older Americans, insurance coverage, finances, family support systems, work status, and retirement planning. Recently, researchers used HRS data on memory and judgment of a large subset of HRS participants to determine trends in cognitive status of those age 70 and older. The researchers found that cognitive impairment dropped from 12.2 percent in 1993 to 8.7 percent in 2002. The study recently has been expanded to include additional key constructs in cognitive aging. NIH also has renewed its program of Centers on the Demography and Economics of Aging to foster research in the demography, economics, and epidemiology of aging and to promote the use of important datasets in the field. The achievements of this program in past years were recognized in September 2008 by the Heidelberg Award for Significant Contributions to the Field of Gerontology, a triennial international competition.

- For more information, see <http://hrsonline.isr.umich.edu>
- For more information, see <http://agingcenters.org>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIA)

Detection, Treatment, and Survivorship of Childhood Cancers: NIH has several ongoing programs to improve detection and treatment of childhood cancers, including the work of the NCI Pediatric Oncology Branch, the Childhood Cancer Survivors Study (CCSS), and the Pediatric Brain Tumor Consortium. Several of these programs are in collaboration with the Children's Oncology Group (COG). A recent COG study discovered that genetic alteration of the IKZF1 gene is associated with

very poor outcomes in patients with B-cell progenitor acute lymphoblastic leukemia (ALL). These results should improve risk stratification for ALL patients, helping to ensure that those with high-risk disease receive treatment of appropriate intensity and sparing low-risk patients unnecessary toxic effects. The Therapeutically Applicable Research to Generate Effect Targets (TARGET) initiative is cataloguing alterations in gene expression, gene sequences, and copy number of chromosome segments in pediatric cancers to discover cancer-specific changes. TARGET data are made available to the research community through a Web portal. TARGET researchers have discovered genomic alterations in pediatric ALL that are predictive of relapse and have identified activating mutations in a tyrosine kinase gene family for which small molecule inhibitors are available. Neuroblastoma TARGET specimens were used to confirm that approximately 10 percent of high-risk neuroblastoma cases have activating mutations in another tyrosine kinase, and a pediatric Phase I trial of an inhibitor of this kinase has been developed. The success of the TARGET approach in identifying novel therapeutic targets for ALL and neuroblastoma supports extension of this approach to other childhood cancers.

- For more information, see <http://www.cancer.gov/cancertopics/coping/childhood-cancer-survivor-study>
- For more information, see <http://www.survivorshipguidelines.org>
- For more information, see <http://home.ccr.cancer.gov/oncology/pediatric/>
- For more information, see <http://www.pbtc.org/>
- For more information, see http://www.cancer.gov/NCICancerBulletin/NCI_Cancer_Bulletin_031808
- For more information, see <http://target.cancer.gov>
- This example also appears in Chapter 2: *Cancer*
- (E/I) (NCI) (ARRA)

Epidemiologic Studies of Osteoporosis: NIH supports several prospective cohort studies, including the Study of Osteoporotic Fractures (SOF) in women and Mr. OS, a study of osteoporosis and other age-related diseases in men. The studies, which have been underway since 1986 and 1999, respectively, identified characteristics associated with fracture risk in older Americans. Assessing risk is important because the devastating consequences of low bone mass can be prevented. For example, simple changes to a person's home (e.g., adding more lights, removing clutter) can prevent falls. A balanced diet and modest exercise build bone strength, and medications can slow disease progression. SOF, Mr. OS, and other studies are providing information about osteoporosis diagnosis, treatment, and prevention. SOF and Mr. OS reinforced a notion, outlined in the Surgeon General's 2004 report on Bone Health and Osteoporosis, that older people who have a fracture should be tested for osteoporosis—even if the fracture occurred because of a traumatic injury (e.g., a fall off a ladder or an auto accident) that could hurt a healthy young person. Mr. OS is generating data that the U.S. Preventive Services Task Force can incorporate into guidance on using bone mineral density to assess fracture risk. Scientists using data from the Framingham Osteoporosis Study recently reported that men and women who consumed the most vitamin C had fewer hip fractures than those who consumed less vitamin C—a finding that may have implications for the recommended intakes established for vitamin C. Women's Health Initiative investigators demonstrated that low blood levels of vitamin D, which helps the body absorb calcium from food, also is associated with hip fracture risk.

- Cawthon PM, et al. *J Bone Miner Res* 2009;24(10):1728-35. PMID: 19419308. PMID: PMC2743283.
- Cauley JA, et al. *Ann Intern Med* 2008;149(4):242-50. PMID: 18711154. PMID: PMC2743412.
- Mackey DC, et al. *JAMA* 2007;298(20):2381-8. PMID: 18042915.

Sahni S, et al. *Osteoporos Int* 2009;20(11):1853-61. PMID: 19347239. PMCID: PMC2766028.

- For more information, see http://www.niams.nih.gov/News_and_Events/Press_Releases/2007/11_28.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/low_vitD_hip_fracture.asp
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIAMS, NCRR, NHLBI, NIA)

Fetal Alcohol Effects: The developing embryo and fetus is very vulnerable to the adverse effects of alcohol. Since Fetal Alcohol Syndrome was first recognized around 1970, NIH has supported research on outreach to pregnant women for identification and intervention of risky drinking; research to enhance our ability for early identification of and interventions with prenatal alcohol-affected children; research exploring nutritional and pharmacological agents that could lessen alcohol's adverse effects on the developing embryo/fetus; and research on how alcohol disrupts normal embryonic and fetal development. For example, a recent study with rats showed that choline, an essential nutrient, was found to effectively reduce the severity of some fetal alcohol effects, even when administered after the ethanol insult was complete. NIH also is investing in a large-scale prospective study looking at prenatal alcohol exposure along with other maternal risk factors in adverse pregnancy outcomes. Following a 3-year feasibility study, NIH established the Prenatal Alcohol, Sudden Infant Death Syndrome, and Stillbirth (PASS) Research Network, a multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study prospectively will follow 12,000 pregnant, high-risk, American Indian and South African women and their infants until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

- For more information, see <http://www.nichd.nih.gov/research/supported/pass.cfm>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIAAA, NICHD)

Following up on the Multimodal Treatment Study of Children with ADHD (MTA): Children with attention deficit hyperactivity disorder (ADHD), the most common of the psychiatric disorders that appear in childhood, often raise great concern from their parents and teachers because of their inability to focus on or finish tasks. Over time, these children may develop other emotional problems, including mood disorders, loss of self-esteem, and substance abuse. To address these issues, NIH is sponsoring an ongoing, multisite, follow-up of children from the MTA study—a treatment trial of nearly 600 ADHD-diagnosed elementary school children. Findings from the original MTA showed that long-term combination treatment (medication and psychosocial/behavioral treatment), as well as medication-management alone, significantly were superior to intensive behavioral treatments and routine community care in reducing ADHD symptoms. In the follow-up study (n = 485 10-13 year olds), children from this cohort and others who received similar pharmacotherapy were assessed for substance abuse outcomes. The study found that despite treatment, children with ADHD showed significantly higher rates of delinquency and substance abuse. Follow-up of the MTA sample is continuing as the participating children go through adolescence and enter adulthood.

- Molina BS, et al. *J Am Acad Child Adolesc Psychiatry* 2009;48(5):484-500. PMID: 19318991.
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0028.html>
- For more information, see <http://www.drugabuse.gov/CTN/protocol/0029.html>
- For more information, see <http://www.nida.nih.gov/ResearchReports/comorbidity/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDA, NIMH)

Insights into the Molecular Interplay Governing Formation of Cranial Sensory

Ganglia: The developmental biology underlying sensory nerve development is fascinatingly intriguing. Take the trigeminal ganglion, which is responsible for touch, pain, and temperature sensation for most of the face. How do precursor cells self-organize in the embryo to produce an anatomically correct sensory network connecting to the central nervous system? Many of the answers are wired into the molecular circuitry of two transient embryonic cell types called neural crest cells and ectodermal placodes. They interact during embryonic development to differentiate into the nerve cells that form the trigeminal ganglion. But virtually nothing is known about the molecular interplay that mediates this interaction. It is a biological puzzle with no known pieces. Now NIH grantees have introduced the first two pieces of the puzzle. They demonstrated in animal studies that the cranial subtype of neural crest cells express the protein Slit1 on their surface during their programmed migration to the trigeminal-forming ectodermal placodes. Meanwhile, as the trigeminal placode cells follow their developmental program, they express on their surface the Robo2 protein, which is the receptor for the Slit1 protein. The Robo2-Slit1 connection, like fitting a hand in a glove, mediates the interaction of neural crest and trigeminal placode cells during the formation of sensory ganglia. When the scientists disrupted one or both molecular signals, the resulting sensory ganglia were abnormal. The teams' findings are important to understanding the mechanisms that regulate formation of the sensory nervous system and thus provide potential targets for identifying the causes of congenital sensory disorders involving the neural crest cell population.

- Shiau CE, et al. *Nat Neurosci* 2008;11(3):269-76. PMID: 18278043.
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/Archive/archive2008/April/TrigeminalGanglion.htm>
- For more information, see http://www.ncbi.nlm.nih.gov/pubmed/18278043?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDCR)

Intellectual and Developmental Disabilities: Intellectual and developmental disabilities (IDD) have serious, life-long effects on cognitive and adaptive development. NIH supports research to improve functioning for individuals who have IDD and to understand the underlying genetic processes to prevent these conditions. For example, NIH supports 14 IDD Research Centers to advance diagnosis, prevention, treatment, and amelioration of IDD. Because the centers have developed core research resources in genetics, proteomics, and clinical infrastructure, they also provide support for researchers in the Fragile X Syndrome (FXS) Research Centers, Rare Disease Cooperative Centers, and Autism Centers. NIH-supported researchers also are conducting a new study to design and

prepare to implement a large multistate study of infants with FXS and their families. The research project goal is to determine the incidence of FXS in the United States, develop screening procedures, address ethical and practical issues related to screening status, and conduct studies on infant development and family adaptation. Also, NIH recently developed a Down syndrome research plan to advance our understanding and speed development of new treatments for the condition—the most frequent genetic cause of mild-to-moderate intellectual disability and associated medical problems.

- For more information, see <http://www.nichd.nih.gov/about/org/cdbpm/mrdd/supported/index.cfm>
- For more information, see http://www.nichd.nih.gov/news/resources/spotlight/012208_research_plan_down_syndrome.cfm
- (E) (NICHD, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, NINDS)

Learning Math and Science: Educators, university leaders, and scientists have called for evidence-based interventions to improve U.S. students' understanding and achievement in mathematics, science, engineering, and technology (STEM). NIH is committed to discovering how children learn and use knowledge, what factors enable this learning, and what can derail learning and/or cause learning disabilities. The NIH Mathematics and Science Cognition and Learning program supports both basic and intervention research in all aspects of quantitative learning, mathematical thinking, and problem-solving, as well as disorders of impaired math learning. Similarly, NIH supports research in how children and adults develop scientific reasoning and learn scientific principles, and how they choose science- and math-based explanations of real-world events over other explanations. To maintain U.S. leadership in technological advances around the world, research on factors that affect the selection of and advancement in STEM vocations also is being supported. Also, in partnership with other relevant Federal agencies, such as the Department of Education and the National Science Foundation, NIH participates in a national mathematics and science initiative and advises on the best use of scientifically based research on teaching and learning these critical subjects.

- For more information, see http://www.nichd.nih.gov/about/org/crmc/cdb/prog_mscl/index.cfm
- (E) (NICHD)

Preventing Drug Abuse in Children and Adolescents: Intervening early to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact and improve the trajectory of a young life. NIH is using a multipronged approach to achieve more effective substance abuse prevention by: (1) developing novel strategies, (2) exploring long-term and crossover effects of proven programs, and (3) improving adoption and implementation of evidence-based approaches. Innovative ideas being explored include physical activity to counter drug use, interactive Web-based technologies to engage young people, and brain imaging results to better target media messages. NIH also is building on proven methods such as universal prevention programs, which can reduce an array of risk behaviors, including substance abuse. These programs typically target behaviors appropriate to a child's developmental stage and have been shown to achieve long-term effects. For example, fifth graders who participated in the school-based prevention program "Positive Action" as first graders were about half as likely to engage in substance abuse, violent behavior, or sexual activity as those who did not. Similarly, exposure to the "Good Behavior Game," designed to reduce aggressive, disruptive behavior in first and second grade classrooms, led to fewer drug and alcohol disorders,

lower rates of regular smoking, less antisocial personality disorder, and reduced delinquency and violent crime in young adults. However, the development of evidence-based prevention programs is meaningless unless they are adopted by communities. Therefore, NIH also is striving to increase implementation of successful prevention approaches in U.S. schools and communities.

- Beets MW, et al. *Am J Public Health* 2009;99(8):1-8. PMID: 19542037.
- Kellam SG, et al. *Drug Alcohol Depend* 2008;95 Suppl 1:S5-S28. PMID: 18343607. PMID: PMC2512256.
- Spoth R, et al. *Am J Prev Med* 2007;32 (5):395-402. PMID: 17478265.
- For more information, see <http://www.nida.nih.gov/scienceofaddiction/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NIDA)

Promising Clinical Trials of Gene Transfer for Severe Childhood Eye Disease: Leber congenital amaurosis (LCA) is an early-onset, severe retinal disease that results from mutations in any 1 of 13 genes. One form of LCA results from mutations in a gene called RPE65. In 1993, NIH intramural scientists discovered that RPE65 plays a key role in the visual cycle, the set of biochemical interactions that converts light into an electrical signal to initiate vision. Mutations in RPE65 were found to disrupt the visual cycle, resulting in LCA and blindness. Retinal cells in children with LCA remain viable for several years, providing a window of opportunity to intervene therapeutically. An NIH-supported Phase I clinical trial of RPE65 gene transfer in LCA found the treatment is safe and that visual function improved. Two other independent Phase I clinical trials of RPE65 gene transfer also found evidence of visual improvement, but further work is needed to develop the therapeutic potential fully. Ongoing studies are exploring the range of therapeutic doses in adult and adolescent patients as well as rigorous evaluation of the effectiveness of this treatment. Gene transfer is particularly well-suited to the treatment of eye disease. This clinical trial is an important step in treating LCA and in establishing proof-of-concept for gene transfer as a viable therapy for eye disease.

- Cideciyan AV, et al. *Proc Natl Acad Sci U S A* 2008;30;105(39):15112-7. PMID: 18809924. PMID: PMC2567501.
- For more information, see <http://www.pnas.org/content/105/39/15112.long>
- For more information, see <http://www.nei.nih.gov/lca/>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (E) (NEI)

Providing Science-Based Oral Health Information: NIH provides science-based oral health information tailored to meet specific needs. Two examples are described here.

- *Practical Oral Care for People with Developmental Disabilities:* Finding dental care in the community is challenging for people with developmental disabilities. Many dentists do not feel trained sufficiently to provide services to people with special needs. To help increase access to dental care, NIH developed a series of publications to equip general dentists with information they need to deliver quality oral care to persons with developmental disabilities. The series includes continuing education (CE) programs for dentists and dental hygienists and a guide for caregivers describing their important role in maintaining good oral health for their family member or client. The modules are so popular that NIH has extended the CE credit through 2011.
- *Spanish-Language Oral Health Website:* The Special Care Dentistry Association partners with

NIH in this important health education outreach—Spanish-Language Oral Health Website. This new Spanish-language website tailored for U.S. Hispanics/Latinos increases Spanish speakers' access to science-based oral health information. The site recently was tested in two cities; participants were Spanish-dominant and bilingual Latinos with backgrounds from different countries of origin and with varying levels of education. The test was to ensure the new website is understandable, credible, and attractive to the intended audience. Other goals included understanding the approach Latinos take when seeking health information online, what they think of the quality of online health information, and whether there are significant differences between Spanish-dominant and bilingual individuals.

- For more information, see <http://www.nidcr.nih.gov/OralHealth/Topics/DevelopmentalDisabilities/>
- For more information, see <http://www.nidcr.nih.gov/espanol>
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*
- (O) (NIDCR, NICHHD)

Researchers Discover Why Mammalian Teeth Form in a Single Row: Why do mammals develop a single row of teeth whereas other vertebrates, such as sharks, can develop multiple rows of teeth? Researchers studying mutations in the genes of mice that develop teeth serving no apparent function may have solved the mystery. Most of the mutations under study caused the mice to develop the extra teeth within the space between the normal incisor and the normal first molar. Since tooth buds normally develop within this part of the developmental field but later regress, these genetic alterations did not alter the normal plane within which teeth developed. However, one particular mutation had a different result. The researchers found that a knockout mutation (i.e., elimination) of a gene known as Odd-skipped related 2 (Osr2) also resulted in the production of extra teeth, but strikingly, these teeth developed outside the usual plane, on the tongue side of the normal molars, suggesting that the mutation results in an expansion of this developmental field in the affected mice. Supporting this theory, the knockout mice (i.e., mice lacking Osr2) have spatially expanded expression of other genes involved in tooth development. That suggests that normal Osr2 acts to restrict tooth development to within its usual, single-row plane. Previous work from this group discovered the Osr2 gene and demonstrated that it is a novel regulator of palate formation. The current study demonstrates that Osr2 function also is critical to the patterning of tooth formation and sheds light on the restriction of teeth to a single row in mammals. Osr2 function may be an important consideration for researchers seeking to grow replacements eventually for lost teeth in adults.

- Zhang Z, et al. *Science* 2009;323:1232-4. PMID: 19251632. PMCID: PMC2650836.
- For more information, see <http://www.nidcr.nih.gov/Research/ResearchResults/ScienceBriefs/CurrentSNIB/Marc h/SingleRow.htm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (NIDCR)

Scientists Demonstrate Hematopoietic Stem Cells' Role in Forming the Stem Cell

Niche: Stem cells are important in all multicellular organisms because they have the ability to develop into different kinds of specialized cells. Outside of the organism, researchers can grow stem cells in specific cultures and observe the development of specialized cells. Blood-forming stem cells, known as hematopoietic stem cells (HSCs), are controlled by the hematopoietic stem cell niche, which is

located in the bone marrow. Bone-forming cells called osteoblasts are known to play a central role in establishing the HSC niche; however, it is unclear whether HSCs in turn control the differentiation of stem cells that become osteoblasts. Although such interactions in the niche have been proposed, at present there is insufficient direct experimental evidence to define the relationship between HSCs and osteoblast formation. In this work, a group of investigators addressed the role of HSCs in the differentiation of osteoblasts. Using mice, they co-cultured HSCs with stem cells that become osteoblasts, and demonstrated that HSCs can indeed affect the differentiation of cells into osteoblasts. Further, the investigators found that the specialization or differentiation into osteoblasts could be influenced by the age and physical condition of the mice. These findings suggest that HSCs may serve as an important therapeutic target for controlling bone formation and repair. In particular, it should be possible to develop therapeutic agents that specifically target HSCs for treatment of a variety of bone defect such as osteoporosis, nonhealing bone and tooth defects, and congenital bone abnormalities.

- Jung Y, et al. *Stem Cells* 2008;26(8):2042-51. PMID: 18499897.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDCR)

The Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development:

An estimated 20 million children under 5 are severely malnourished, leaving them more vulnerable to illness and early death, according to the World Health Organization. Poor nutrition in early childhood may lead to cognitive defects and poor physical development, may increase susceptibility to and severity of infections, and may diminish the effectiveness of childhood vaccines. Focusing on the interactions between communicable and noncommunicable conditions, in 2009, the Foundation for the National Institutes of Health, together with NIH, launched a 5-year study to investigate the links between malnutrition and intestinal infections and their effects on children in the developing world. With the establishment of this remarkable public-private partnership, the project aims to shed light on critical questions related to the interaction between infections and growth and development. This large-scale, Gates-funded, NIH-led, \$30 million project will support collaborative, multisite studies of malnutrition and enteric infections involving sites in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, and Tanzania. In addition to making critical discoveries that will help save the lives of the world's youngest and poorest children, the main objective of this research network is to create a standardized set of epidemiological tools to accurately study the links between intestinal infections and gut physiology as risk factors for malnutrition across a number of diverse sites in the developing world. This research effort will be conducted in collaboration with universities in the United States and institutions in the developing world.

- For more information, see <http://origem.info/malnutritionstudy/>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*
- (O) (FIC, FNIH)

The Role of Development in Drug Abuse Vulnerability: NIH supports animal, clinical, and epidemiological research across the lifespan to examine how developmental stage may influence drug abuse vulnerability or protection. The discovery of a protracted period of brain changes during early development and beyond has been critical to understanding the role of brain maturation in decision-making processes and responses to stimuli, including early (e.g., in utero) exposure to drugs. Adolescence has emerged as a particularly vulnerable period, during which an immature brain circuitry

can translate into a preponderance of emotional reactivity (vs. higher cognitive control) that gives rise to the impulsive characteristics of many teenagers. This in turn may lead to dangerous risk-taking, such as experimenting with drugs that ultimately can lead to addiction. Using both animal models and clinical research, scientists are beginning to understand how environmental variables can play a key role in shaping brain maturation trajectories. In this regard, imaging, genetic, and epigenetic tools are helping interpret the effects of myriad environmental influences, such as quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics on brain development and behavior. In addition, the field of social neuroscience is harnessing the power of multidisciplinary approaches to tease apart these multilevel phenomena to better understand, for example, the neural mechanisms of peer pressure, the connections between chronic stress and risk of drug abuse initiation, and the impact that different early rearing environments can have on gene expression and behavior.

- For more information, see <http://www.nida.nih.gov/tib/prenatal.html>
- For more information, see <http://www.nida.nih.gov/scienceofaddiction/>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*, Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (NIDA, NICHD) (GPRA)

Underage Drinking Research Initiative: In 2004, NIH launched its Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence—all framed within the context of overall human development. Activities and accomplishments in 2008 and 2009 include: (1) working with the Office of the Surgeon General to disseminate *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking*, including state roll-outs in Oklahoma, Ohio, Nebraska, Wyoming, Montana, Maryland, and Rhode Island (in addition to the six held in 2007); (2) continuing to convene scientific meetings of experts to advance underage drinking research. A series of meetings focusing on the development of guidelines and recommendations for screening children and adolescents for risk for drinking, alcohol abuse, and alcohol use disorders continued in 2008-2009; (3) issuing RFAs and program announcements (PAs), including "Limited Competition: Underage Drinking: Building Health Care System Responses (Phase II)" (RFA-AA-09-001) and "Alcohol, Decision-Making, and Adolescent Brain Development" (PA- 09-097 (R01) and PA-09-096 (R21)); (4) published "A Developmental Framework for Underage Alcohol Use"; and (5) published a *Pediatrics* supplement of seven developmentally focused papers covering a broad range of underage drinking topics.

- A Developmental Perspective on Underage Alcohol Use. *Alcohol, Research and Health* 2009;32(1). Available at: <http://pubs.niaaa.nih.gov/publications/arh321/toc32-1.htm>. Masten AS, et al. *Pediatrics* 2008;121 Suppl 4:S235-51. PMID: 18381492. Available at: http://pediatrics.aappublications.org/cgi/reprint/121/Supplement_4/S235.
- For more information, see <http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E, O) (NIAAA)

Building a Longitudinal Mental Health Tracking System: NIH has laid the initial groundwork to develop a mental health tracking system that will provide epidemiologic information on mental disorders on a continuing basis. By working with Federal agencies that currently conduct large-scale, ongoing national surveys, and adding detailed measures of mental health status, functioning, and service use, NIH will leverage existing resources to collect important mental health information in a cost-efficient manner. The longitudinal nature of the resulting data will provide NIH the ability to track the prevalence, incidence, severity, correlates, and trajectories of mental disorders, as well as related service use and outcomes, over time. The resulting data also could provide important information on key subgroups (e.g., racial/ethnic populations, people with autism) and geographic areas of varying sizes (e.g., states, counties). These data are critical for targeting future research activities and ensuring the effectiveness of delivered interventions.

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIMH)

EARLI, the Early Autism Risk Longitudinal Investigation: EARLI, the Early Autism Risk Longitudinal Investigation, comprises a network of leading autism researchers from three regions across the country. EARLI is following a cohort of 1,200 mothers of children diagnosed with autism who are pregnant or planning a pregnancy. The EARLI network will study how genetics and environmental factors work together to cause autism by studying families who already are affected by autism. Data will be collected prospectively via clinical assessment, interviews, self-reports, medical record review, home environment assessments, and biologic samples that will be used in current analysis and stored for future studies. Planned analyses include a determination of whether in utero exposure to organic pollutants such as polychlorinated biphenyls (PCBs), brominated diphenyl ethers (BDEs), and persistent organic pollutants (POPs) is associated with autism risk.

- For more information, see <http://earlistudy.org>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIEHS)

Population Research: Given the Nation's increasing diversity and changing demographics, it is critical to understand how trends in such areas as immigration, fertility, marriage patterns, and family formation affect the well-being of children and families. NIH research in these areas allows policymakers and program planners to better address public health needs. For instance:

- The Fragile Families and Child Well-Being Study follows children born to unmarried parents to assess how economic resources, father involvement, and parenting practices affect children's development.
 - The New Immigrant Survey follows the first nationally representative sample of legal immigrants to the United States, providing accurate data on legal immigrants' employment, lifestyles, health, and schooling before and after entering the country.
 - Several NIH Institutes are supporting The National Longitudinal Study of Adolescent Health, which integrates biomedical, behavioral, and social science data to discover the pathways that lead to health and/or disease in adulthood.
- For more information, see <http://www.cpc.unc.edu/addhealth/>

- For more information, see <http://nis.princeton.edu/index.html>
- For more information, see <http://www.fragilefamilies.princeton.edu/index.asp>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NICHD, NCI, NCMHD, NIA, NIAAA, NIAID, NIDA, NIDCD, NINR, OAR, OBSSR, ORWH)

The Early Childhood Longitudinal Study (ECLS) program: The National Center for Education Statistics, within the Institute of Education Sciences of the U.S. Department of Education, is conducting an ongoing study of a nationally representative sample of children from diverse socioeconomic and racial/ethnic backgrounds who will start kindergarten in 2011. Several Federal agencies, including NIH, are partnering on the study to determine how a variety of home, school, community, and student factors influence the transition of children to school; frame their early school experiences; shape their later school experiences; relate to normal cognitive, social, emotional, and physical child development; and affect academic performance over time. NIH is participating in a field test to work out logistics to determine the feasibility of adding a hearing and vision screening examination in the ECLS. ECLS is the only recent, nationally representative data collection program that enables statistical analysis of relationships between hearing and communication impairments or disorders and subsequent child development from infancy through eighth grade. The intent is to measure the hearing and vision of children during their first year of formal schooling, find out how hearing and vision change as a child grows, establish whether hearing and vision influence other aspects of normal child development, and clarify whether academic performance is influenced by hearing and vision. This information can be used then to evaluate how well early identification and intervention strategies were implemented during the birth cohort years from an earlier ECLS study.

- For more information, see <http://nces.ed.gov/ECLS/>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NEI, NIDCD)

The National Children's Study (NCS): NCS promises to be one of the richest information resources available for answering questions related to children's health and development and will form the basis of child health guidance, interventions, and policy for generations to come. The landmark study will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. This extensive research effort will examine factors ranging from those in the natural and man-made environment to basic biological, genetic, social, and cultural influences. By studying children through their different phases of growth and development, researchers will be able to understand better the role of these factors in both health and disease. Specifically, the NCS will identify factors underlying conditions ranging from prematurity to developmental disabilities, asthma, autism, obesity and more. The study is led by a consortium of Federal agencies including NIH, CDC, and the EPA.

- For more information, see <http://www.nationalchildrensstudy.gov>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (I) (NICHD, NIEHS)

Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS): HANDLS is a community-based study to evaluate health disparities in socioeconomically diverse African American and white adults in Baltimore. Planned recruitment of 4,000 participants is more than three-

quarters complete. Scientists are using mobile medical research vehicles to make possible onsite bone density and carotid artery imaging, physical examination and blood sampling, physical and cardiovascular performance, participant interviews, cognitive testing, and psychophysiological testing. HANDLS also will include studies of other variables, including: nutrition, environment and neighborhood effects, genetic make-up, family history, and access to health care. Participants will be followed over a 20-year period to allow researchers to gain insights into the physical, genetic, biologic, demographic, and psychosocial traits that may be most critical for healthy aging.

- For more information, see <http://handls.nih.gov>
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (NIA)

Rehabilitation

Neural Interfaces Program: Neural interfaces are systems that operate at the intersection of the nervous system and an internal or external device, including neural prosthetics. Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. NIH pioneered the development of this technology, beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants, which help people with hearing impairments; respiratory and hand grasp devices for people with spinal cord injuries; and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore voluntary bowel and bladder control and standing to spinal cord-injured persons, allow paralyzed persons to control devices directly from their brains, improve cochlear implants, and improve deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community, now including private sector companies, and represents a cooperative effort among several ICs, which also coordinate their efforts with programs that now are underway in the Department of Veterans Affairs and Department of Defense.

- For more information, see <http://www.ninds.nih.gov/funding/research/npp/index.htm>
- For more information, see <http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*
- (E) (NINDS, NEI, NIBIB, NICHD, NIDCD)

Traumatic Brain Injury Program: Traumatic brain injury (TBI) presents enormous challenges because TBI affects so many people and can compromise virtually any human ability, depending on which parts of the brain are damaged. NIH research ranges from how TBI causes immediate and delayed damage to brain cells, to development of markers of damage, through large clinical trials to test interventions. Multicenter clinical trials now are testing hypothermia (cooling) in children and use of the hormone progesterone to minimize damage in adults. In addition, NIH launched a program to collect data on the use of multidrug combinations to better treat traumatic brain injury. Because the high rate of TBI among military personnel in Afghanistan and Iraq presents a special concern, a Federal Interagency TBI Research group now coordinates among NIH, VA, DOD, and other agencies. Trans-agency workshops have focused on TBI classification (Oct. 2007), combination therapies for TBI (Feb. 2008), opportunities and challenges of blast injury-induced TBI (April 2008), and "Integrated

Research on Psychological Health and TBI: Common Data Elements" (March 2009). NIH is working with CDC on how to better track TBI in former military personnel and on evaluating the effectiveness of rehabilitation for TBI. The NINDS intramural research program has worked with the VA and DOD for many years on long-term neuropsychological outcomes of TBI in Vietnam veterans, and now in Iraq veterans. The NIH Intramural Research Program also is partnering now with the Uniformed Health Services University of the Health Sciences Center in the joint Center for Neuroscience and Regenerative Medicine, whose extensive TBI research programs range from molecular studies to understanding TBI mechanisms through rehabilitation and outcomes research.

- For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Neurological_Effects_of_Blast_Injury_Workshop.htm
- For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Combination_Therapies_for_Traumatic_Brain_Injury_Workshop.htm
- For more information, see http://www.ninds.nih.gov/news_and_events/proceedings/Classification_of_Traumatic_Brain_Injury_Workshop.htm
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-003.html>
- For more information, see <http://www.usuhs.mil/cnrm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (E, E/I) (**NINDS**, CC, NICHD, NIMH, NINR)

Prostheses to Restore Lost Function: Many veterans return home with significant injuries to their extremities, including loss of limbs. Through multidisciplinary partnerships between engineers, clinicians, scientists, and industrial partners, NIH investigators are developing new and novel technology for assistive rehabilitation, such as electrodes for neural and muscular recordings, networked implantable systems for functional electrical stimulation, robotics for rehabilitation, and brain computer interface systems for communication and control. For example, next-generation hand and arm prosthesis systems controlled by intact muscle recordings will be able to produce fine finger movements and provide to the user the sensation of position and force applied to an artificial hand. Other examples include multifunctional stimulation systems that allow spinal cord-injured subjects to change posture, stand, step, and control hand and arm function.

- Weir RF, et al. *IEEE Trans Biomed Eng* 2009;56(1):159-71. PMID: 19224729.
- This example also appears in Chapter 3: *Technology Development*
- (E) (**NIBIB**)

Center for Neuroscience and Regenerative Medicine: The Center for Neuroscience and Regenerative Medicine (CNRM) is a collaborative initiative between NIH and the U.S. Department of Defense (DOD). The center's research mission is to discover methods to better intervene and prevent the long-term consequences resulting from traumatic brain injury (TBI). To increase research capabilities, the United States Congress established the CNRM as a collaborative intramural program and appropriated funds to the DOD for implementation. CNRM will study combat casualties cared for at Walter Reed Army Medical Center (WRAMC) and the National Naval Medical Center (NNMC) using advanced molecular and neuroimaging technology at the NIH CC. The CNRM seeks to serve as the catalyst for collaboration, innovation, and advancement of knowledge of the incidence of TBI and the

identification of interdisciplinary approaches to assess TBI and promote recovery. CNRM research programs address the full spectrum of TBI, including the effect of high anxiety and the concurrent development of post-traumatic stress disorder with TBI. In addition, the center will evaluate civilian patients with brain injury following trauma, to understand the relationship between military and civilian brain injury in patients as well as in preclinical models. CNRM research programs focus on (a) diagnostics and imaging, (b) biomarkers, (c) neuroprotection and models, (d) neuroregeneration, (e) neuroplasticity, and (f) rehabilitation and evaluation. The program leverages the strengths of NIH in neurosciences and neuroimaging together with DOD experience in brain trauma, neuroregeneration, and modeling.

- For more information, see <http://www.usuhs.mil/cnrm>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System*
- (I) (CC, NINR, NIMH, NINDS)

Advancing Research on Prosthetics: NIH is investing strategically to develop improved prosthetic devices that can help soldiers and other individuals who have lost limbs or who have suffered a traumatic injury resume normal activities. Earlier research in movement control paved the way for a new nerve-muscle graft procedure that enables amputees to have more natural control of a prosthetic device. NIH now is stimulating the development of advanced methods to eliminate infection when lower limb prostheses are directly attached to bones. And, through Small Business Innovation Research Awards, NIH continues to support research to develop cutting edge sensors for prosthetic devices and virtual reality systems to enhance rehabilitation. In response to the rise in the number of individuals who need prosthetic and orthotic devices, NIH also is encouraging research on the development of outcome measures to help assess the effectiveness of those devices. This research ultimately will provide clinicians the information they need to optimize rehabilitation and quality of life for amputees and an aging population.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-012.html>
- (E) (NICHD)

Laryngeal Tissue Regeneration: The vocal folds (also referred to as vocal cords) are two elastic bands of muscle tissue located in the larynx (voice box) directly above the trachea (windpipe). The vocal folds produce voice when air held in the lungs is released and passed through the closed vocal folds, causing them to vibrate. Vocal fold scars can result from injury or inflammation, or as a consequence of surgery to remove vocal fold nodules or polyps. The scars increase vocal fold stiffness and reduce their ability to vibrate. An individual with scarred vocal folds may have a hoarse, breathy, or low-pitched voice. NIH-supported scientists have developed a new class of soft gel material to serve as a scaffold to encourage regeneration of vocal fold tissue. Specific particles within the material also can be modified to bind and slowly release therapeutic drugs within the vocal folds as a way to further encourage regeneration of the native tissue. Scientists now are testing this new material to learn more about what types of changes (to particle size, distribution, etc.) will optimize tissue regeneration. Once the gel is optimized in laboratory tests, it will offer the hope of treatment for individuals whose vocal folds have been damaged due to scarring.

- Jha A, et al. Structural Analysis and Mechanical Characterization of Hyaluronic Acid-Based Doubly Cross-Linked Networks. *Macromolecules* 2009;42:537-46.

- For more information, see <http://www.nidcd.nih.gov/health/voice/takingcare.htm>
- For more information, see <http://pubs.acs.org/doi/abs/10.1021/ma8019442>
- (E) (NIDCD)

Stem Cells and Regenerative Medicine: Stem cells are able to renew themselves and generate progeny that differentiate into more specialized cells. They play critical roles in organism development, and some are essential for normal homeostasis and tissue repair. NIH has made a significant investment in stem cell research. One NIH-supported study showed that the sex of cells in a subpopulation of muscle-generating stem cells in adult mice can influence their capacity to repair tissue considerably. This finding could lead to future therapies for various diseases, including muscular dystrophy. A collaboration between NIH Intramural researchers and those at Walter Reed Army Medical Center discovered that waste tissues from surgery, removed to promote healing of orthopaedic injuries and war-traumatized muscle, contain large numbers of progenitor cells that are capable of differentiating into bone, fat, and cartilage cells. They could be used as a cell source for regenerative medicine therapies, and thereby avoid additional surgery to harvest cells. NIH has partnered with the Department of Defense on an initiative to speed treatments to wounded soldiers abroad, and civilian trauma victims and burn patients in the United States. This collaboration has resulted in the establishment of the new Armed Forces Institute of Regenerative Medicine (AFIRM). The AFIRM-led program will focus on regrowing fingers, repairing shattered bones, and restoring skin to burn victims with genetically matched skin, to pave the way for commercial products in the near future. Hair follicles are useful models for organ regeneration. Recent discoveries have been made in the molecular processes that govern the growth of hair follicle stem cells, which are a source for newly formed hair follicles.

- Deasy BM, et al. *J Cell Biol* 2007 Apr 9;177(1):73-86. PMID: 17420291. PMCID: PMC2064113.
- Jackson WM, et al. *J Tissue Eng Regen Med* 2009 Feb;3(2):129-38. PMID: 19170141.
- Plikus MV, et al. *Nature* PMID: 18202659. PMCID: PMC2696201.
- Horsley V, et al. *Cell* 2008 Jan 25;132(2):299-310. PMID: 18243104. PMCID: PMC2546702.
- Nesti LJ, et al. *J Bone Joint Surg Am* 2008;90(11):2390-8. PMID: 18978407. PMCID: PMC2657299.
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2007/cell_sex_and_stem_cell.asp
- For more information, see http://www.niams.nih.gov/News_and_Events/Spotlight_on_Research/2009/progenitor_cells.asp
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*, Chapter 3: *Clinical and Translational Research* and Chapter 3: *Technology Development*
- (E/I) (NIAMS, NIA, NIAID, NIBIB)

Bioactive Nanostructures for Neural Regeneration: Spinal cord injury (SCI) often leads to permanent paralysis and loss of sensation below the site of injury because of the inability of damaged axons to regrow across the injury site in adults. Nanomaterials built from a family of self-assembling molecules may offer hope for treating serious injuries, such as spinal cord injury according to new results from NIH research. Recently, an NIH-supported research group developed peptide amphiphile (PA) molecules that self-assemble in vivo into supramolecular nanofibers and tested them on mouse

models of spinal cord injury. In this work, in vivo treatment with the PA nanofibers, after SCI, reduced cell death and promoted regeneration of both motor fibers and sensory fibers through the lesion site. Treatment with the PA also resulted in significant behavioral improvement. These observations demonstrate that it is possible to inhibit glial scar formation and to facilitate regeneration after SCI using bioactive three-dimensional nanostructures displaying high densities of neuroactive epitopes on their surfaces.

- Tysseling-Mattiace VM, et al. *J Neurosci* 2008;28(14):3814-23. PMID: 18385339. PMCID: PMC2752951.
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Technology Development*
- (E) (NIBIB)

Other Notable Examples

Clinical Research Networks: Clinical research is essential for translating laboratory findings into evidence-based interventions targeting an array of public health concerns. Many research programs involve collaborative networks, drawing scientists together to bring the benefits of clinical research to high-risk populations, hard-to-reach communities, and individuals with rare or understudied conditions. Among such networks that have generated significant findings to advance medical practice and improve public health are the Maternal and Fetal Medicine Network, Neonatal Research Network, Obstetric Pharmacology Research Network, Pediatric Critical Care Research Network, Pelvic Floor Disorders Network, Traumatic Brain Injury Clinical Trials Network, and Global Network for Women's and Children's Health Research.

- For more information, see <http://www.bsc.gwu.edu/mfmu/index.html>
- For more information, see <https://neonatal.rti.org>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-002.html>
- For more information, see <http://www.cpccrn.org>
- For more information, see <http://www.pfdnetwork.org>
- For more information, see <http://www.tbi-ct.org/>
- For more information, see <http://gn.rti.org/about/index.cfm>
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (NICHD, FIC, NCCAM, NCI, NIDCR, ORWH)

Addressing Drug Abuse and Comorbidities in Returning Vets and Their

Families: Sustained U.S. combat operations in Afghanistan and Iraq have resulted in military personnel experiencing increased numbers and lengths of deployments and greater exposure to traumatic stressors. Stress can be a major contributor to both the onset and exacerbation of substance abuse and other mental health problems, and can lead to relapse in former substance abusers. To understand better the intervention needs of this group, NIH in 2009 sponsored a 2-day meeting to formulate a research agenda for conducting addiction prevention and treatment research with military and veteran populations and their families. Collaborators included the U.S. Army Medical Research and Materiel Command, the Department of Defense Health Affairs, the Army Center for Substance Abuse Programs, the Department of Veterans Affairs, and several NIH ICs. Subsequently, a call for studies on trauma, stress, and substance use and abuse among U.S. military personnel, veterans, and their families was issued. It focuses on epidemiology/etiology, screening and identification, and

prevention and treatment of substance use and abuse—including alcohol, tobacco, and other drugs—and associated problems (e.g., PTSD, traumatic brain injury, sleep disturbances, and relationship violence) among U.S. military personnel, veterans, and their families. Further, NIH's National Drug Abuse Treatment Clinical Trials Network (CTN) is developing a protocol concept for the treatment of PTSD and drug abuse/dependence in veteran populations. It is expected that this study will be conducted in clinics participating in the CTN, which include some Veterans Administration hospitals and research facilities.

- For more information, see <http://www.drugabuse.gov/pdf/tib/veterans.pdf>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (NIDA, NCI, NIAAA, NIMH)

Transdisciplinary Tobacco Use Research Centers (TTURCs)—Alcohol Use and

Smoking: Multiple Institutes at NIH are co-funding seven collaborative, transdisciplinary centers to identify familial, early childhood, and lifetime psychosocial pathways related to smoking initiation, use, cessation, and patterns of dependence. Research on genetics of addiction, physiological biomarkers, and the use of advanced imaging techniques can lead to individualized and community approaches for tobacco prevention and treatment. This model demonstrates the feasibility and benefits of scientific collaboration across disciplines and public-private partnerships. Some recent highlights include: For smokers quitting while taking the prescription drug bupropion, the risk of smoking relapse was associated primarily with heavy, rather than with moderate drinking. Interactions between brain pathways activated by nicotine and alcohol may increase the likelihood of drinking in humans who simultaneously smoke and drink, suggesting that drugs that block nicotinic receptors also may help to reduce drinking. Varenicline, an agonist of certain nicotinic acetylcholine receptors, is a smoking cessation medication that has been shown in preclinical research to reduce alcohol drinking. Researchers are testing varenicline in preclinical models of ethanol drinking to determine which nicotinic receptor subtypes are most important. Recently, they found that varenicline reduces alcohol self-administration in heavy-drinking smokers.

- For more information, see <http://dccps.nci.nih.gov/tcrb/tturb>
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 2: *Chronic Diseases and Organ Systems*
- (E) (NIAAA, NCI, NIDA)

Testing for Reproductive Tumors in the National Toxicology Program's

Carcinogenesis Bioassay: Perinatal Dosing: The National Toxicology Program (NTP) evaluates substances for a variety of health-related effects. Two-year studies in laboratory rodents remain the primary method by which chemicals or physical agents are identified as having the potential to be hazardous to humans. In 2006, NTP convened a workshop on Hormonally Induced Reproductive Tumors, Relevance of Rodent Bioassays to discuss the adequacy of rodent models used in the 2-year bioassay for detecting reproductive tumors. The workshop recommended that in utero and lactational exposures could be added to the chronic bioassay depending upon what is known about the mode of action. For detecting tumor types such as testicular germ cell tumors, this recommendation was especially strong. In utero and lactational exposures should be considered for mammary tumor studies if there are any developmental effects associated with a substance under study that involved endocrine tissues, steroid receptor binding, a change in mammary gland

morphology, or altered timing of vaginal opening. NTP has conducted such perinatal exposures on cancer bioassays in the past, but only when there was special justification for such a design to be adopted. A new default design in which dosing will start in pregnancy and be continued throughout life or to the end of a 2-year period now has been adopted unless there is a good scientific reason not to undertake such a study. NTP has initiated studies to obtain data for constructing physiologically based pharmacokinetic (PBPK) models in rodents and nonhuman primates. It is planning studies to explore the long-term consequences of perinatal exposure to Bisphenol A to understand the potential impact to humans of the developmental changes reported in numerous laboratory animal studies. It is hoped that the PBPK models will link information from rodent studies with primate studies, and potentially with human outcomes.

- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
- (O) (NIEHS)

Bisphenol A Exposure and Effects: More than 90 percent of the U.S. population is exposed to low levels of BPA. Exposures may occur through use of polycarbonate drinking bottles and the resins used to line food cans. The NIH National Toxicology Program's (NTP's) Center for the Evaluation of Risks to Human Reproduction conducted an evaluation to determine whether current levels of exposure to BPA present a hazard for human reproduction and/or development. Following this evaluation of existing literature, the NTP expressed "some concern" for effects on the brain, behavior, and prostate gland based on developmental effects reported in some laboratory animal studies using BPA exposures similar to those experienced by humans. NIH is working to address and support research and testing needs identified during the NTP evaluation to understand any potential risks for humans from BPA exposure. In collaboration with scientists at the FDA National Center for Toxicological Research, the NTP has designed and begun studies to evaluate similarities and differences in how rats metabolize BPA in relation to nonhuman primates, and to further understand the long-term health consequences from exposures to low levels of BPA during rodent development. In addition, NIH is providing grant support to the extramural community for studies that focus on investigating possible long-term health outcomes from developmental exposure or chronic exposures to environmentally relevant doses of BPA. Collectively, these studies should address research gaps, reduce uncertainties, and provide perspective regarding any potential risk that BPA poses for public health.

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- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Clinical and Translational Research*
 - (I) (NIEHS)

NIH Strategic Plans Pertaining to Life Stages, Human Development, and Rehabilitation Research

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- [Demographic and Behavioral Sciences Branch Goals and Opportunities, 2002-2006](#)
- [Pregnancy and Perinatology Branch Strategic Plan, 2005-2010, 2003](#)
- [Surgeon General's Conference on the Prevention of Preterm Birth](#)
- [Closing the Gap: A National Blueprint to Improve the Health of Persons with Mental Retardation](#)
- [Child and Adolescent Development Research and Teacher Education: Evidence-based Pedagogy, Policy, and Practice](#)
- [Workshop to Develop an Agenda on Research Settings for Rehabilitation](#)

Branch Reports to Council with Future Scientific Directions:

- [Mental Retardation and Developmental Disabilities \(MRDD\) Branch, Report to the NACHHD Council, June 2005](#)
- [Division of Epidemiology, Statistics, and Prevention Research \(DESPR\), NICHD, Report to the NACHHD Council, September 2005](#)
- [National Center for Medical Rehabilitation Research \(NCMRR\) Report to the NACHHD Council, January 2006](#)
- [Developmental Biology, Genetics and Teratology Branch Report to the NACHHD Council, September 2006](#)
- [Reproductive Sciences Branch, NICHD Report to the NACHHD Council, January 2007](#)
- [Pediatric, Adolescent, and Maternal AIDS Branch \(PAMAB\), NICHD, Report to the NACHHD Council, June 2007](#)
- [Demographic and Behavioral Sciences, NICHD Report to the NACHHD Council, September 2007](#)
- [Demographic and Behavioral Sciences \(DBS\) Branch Long-Range Planning 2006-2007: Highlights from a Panel Discussion](#)
- [Obstetric and Pediatric Pharmacology Branch \(OPPB\), NICHD, Report to the NACHHD Council,](#)

- [January 2008](#)
- [Contraception and Reproductive Health Branch \(CRHB\), NICHD, Report to the NACHHD Council, June 2008](#)
- [Pregnancy and Perinatology Branch \(PPB\), NICHD, Report to the NACHHD Council, September 2008](#)
- [Child Development and Behavior Branch \(CDBB\), NICHD, Report to the NACHHD Council, January 2009](#)
- [Endocrinology, Nutrition, and Growth \(ENG\) Branch Report to Council](#)
- [Intellectual and Developmental Disabilities \(IDD\) Branch Report to Council](#)

National Cancer Institute (NCI)

- [NCI Strategic Plan for Leading the Nation](#)

National Eye Institute (NEI)

- [National Eye Institute Strategic Planning](#)
- [National Plan for Eye and Vision Research \(2004\)](#)
- [Progress in Eye and Vision Research 1999-2006](#)
- [Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation \(2007\)](#)
- [Age-Related Macular Degeneration Phenotype Consensus Meeting Report](#)
- [Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report](#)
- [Report of the Advances in Optical Imaging Symposium](#)

National Institute of Dental and Craniofacial Research (NIDCR)

- [NIDCR Strategic Plan](#)
- [NIDCR Implementation Plan](#)

National Institute on Aging (NIA)

- [Living Long and Well in the 21st Century: Strategic Directions for Research on Aging](#)

National Institute on Drug Abuse (NIDA)

- [NIDA Five-Year Strategic Plan 2009](#)

National Institute on Deafness and Other Communication Disorders (NIDCD)

- [NIDCD Action Plan on Research Careers for Deaf Individuals](#)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- [National Institute on Alcohol Abuse and Alcoholism Five-Year Strategic Plan FY08-13](#)

Recommendations of the NIAAA Extramural Advisory Board (EAB)

- [Fetal Alcohol Spectrum Disorders Research](#)

- [Mechanisms of Behavioral Change](#)

National Institute of Nursing Research (NINR)

- [NINR Strategic Plan: Changing Practice, Changing Lives](#)

Office of Dietary Supplements (ODS)

- [Promoting Quality Science in Dietary Supplement Research, Education, and Communication: A Strategic Plan for the Office of Dietary Supplements, 2004-2009](#)

Trans-NIH Strategic Plans

- [NIH Research Plan on Down Syndrome](#)
(NICHD, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, NINDS)
- [NIH Research Plan on Fragile X Syndrome and Associated Disorders](#)
(NICHD, NIMH, NINDS, NIA, NIDDK, NIGMS, NCI, NIDCD)
- [NIDDK Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan](#)
(CC, CSR, NCCAM, NCI, NCMHD, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)
- [NIH Action Plan for Transplantation Research \(2007\)](#)
(NCI, NHLBI, NIA, NIAAA, **NIAID**, NIAMS, NIBIB, NIDA, NIDCR, NIDDK, NIMH, NINDS)

Interagency Plans

- [2009 Strategic Plan for Autism Spectrum Disorder Research](#)
(NIH [NIMH, NICHD, NIEHS, NIDCD, NINDS]), ACF, CMS, CDC, HRSA, SAMHSA, HHS Office on Disability, U.S. Department of Education)